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# BETAINE AND GLYCOCYAMINE IN TREATMENT OF POLIOMYELITIS*

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THE purpose of this study was to investigate the purported value of betaine and glycocyamine in the treatment of late residual muscular weakness resulting from poliomyelitis.‡ To make the evaluation as objective as possible the strength of the muscles studied was measured by means of a special instrument known as a myodynemeter utilizing a strain gauge with calibrated recording device and standardized test positions that experience in this laboratory had shown to be highly accurate.

## METHOD OF STUDY

Nine patients, all of them co-operative adults, who had had poliomyelitis, with residual weakness, one or more years previously were selected. They had all been treated in the Massachusetts General Hospital and had reached a stage such that increases in muscle function were absent or minimal. Most of them had had myodynemetric tests in the past. The age, sex and date of onset of poliomyelitis are listed in Table 1. One patient was studied who had had infectious polyneuritis several years previously, with residual paralysis of the muscles of both legs.

The control period lasted two or three weeks, and at weekly intervals the muscles to be studied were tested; in all cases force reactions repeatable within 5 pounds were obtained. The patients were then placed on daily medication with betaine and glycocyamine in amounts noted in Table 1, and strength tests were repeated at two-week intervals for six to eight weeks. The patients were told that this was an experimental study to determine as accurately as possible the benefits of the new drugs. Efforts were made not to exhibit any enthusiasm for the drugs on the part of the investigators, to whom all patients were quite well known. All patients were satisfied with the treatment regimen that had previously been instituted for them and had learned to accept some degree of muscle weakness as probably permanent.

## RESULTS

A total of 21 different muscle actions were studied in this group of patients, as follows: wrist flexion and extension; elbow flexion and extension; shoulder internal rotation, vertical and horizontal abduction, extension and flexion; foot dorsiflexion, eversion, inversion and combined dorsiflexion and inversion, knee extension and flexion; and hip flexion, extension, adduction, abduction, internal rotation and external rotation. A total of 76 muscle actions were recorded, since 2 to 13 different muscles were tested in each of these 10 patients. The actual muscle actions for each patient are listed in Table 2.

TABLE 1. *Pertinent Data in Patients Tested.*

| CASE NO. | AGE | SEX | DATE OF ONSET OF POLIOMYELITIS | DAILY DOSE OF GLYCOCYAMINE | DAILY DOSE OF BETAINE |
|---|---|---|---|---|---|
| | yr. | | | gm. | gm. |
| 1 | 31 | M | 1946 | 5.5 | 25 |
| 2 | 24 | F | 1949 | 4.5 | 20 |
| 3 | 37 | M | 1949 | 5.5 | 25 |
| 4 | 27 | M | 1949 | 5.5 | 25 |
| 5 | 17 | F | 1949 | 3.5 | 20 |
| 6 | 19 | F | 1949 | 3.5 | 20 |
| 7 | 17 | M | 1947 | 4.5 | 25 |
| 8 | 20 | M | 1949 | 4.0 | 25 |
| 9 | 27 | F | 1947 | 3.0 | 20 |
| 10* | 51 | M | 1943 | 5.5 | 25 |

*Patient with polyneuritis.

While the patient was on medication the same muscle actions were tested for a total of six to eight weeks. Three separate tests were done for each muscle action on each test day, and a variation of no more than 3 pounds, and often less, was obtained in the three tests. The highest figure before medication was then compared with the lowest figure on the test day in which the highest post-medication figure results were recorded. The actual results in pounds for each muscle action for each patient are given in Table 2, together with the increase or decrease.

The percentage increase in strength of muscles was compared to the number of muscles and the

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percentage of total muscles; 38 per cent of the muscles had less than 10 per cent and 76 per cent less than 20 per cent increase in strength. If a 20 per cent rise is regarded as significant, it can be concluded that 24 per cent of the muscles studied showed a significant increase. Four muscles decreased slightly in strength according to the myodynemetric tests. There was only 1 patient who

TABLE 2. *Results of Muscle Tests.*

| MUSCLE ACTION | GRADE | SIDE | ACTUAL STRENGTH ON LAST TEST | | ACTUAL CHANGE ON LAST TEST |
|---|---|---|---|---|---|
| | | | BEFORE MEDICATION | AFTER MEDICATION | |
| | | | lb. | lb. | |
| **Case 1:** | | | | | |
| Hip adduction | Fair | Right | 32.0 | 54.0 | +22.0 (41%) |
| Hip adduction | Fair | Left | 37.0 | 62.0 | +25.0 (42%) |
| Knee flexion | Good | Right | 38.0 | 44.0 | + 6.0 (14%) |
| Knee flexion | Good | Left | 34.0 | 39.0 | + 5.0 (12.5%) |
| Hip extension | Fair | Left | 44.0 | 43.0 | − 1.0 (−2%) |
| Knee extension | Good | Left | 76.0 | 84.0 | + 8.0 (10%) |
| Knee extension | Good | Right | 76.0 | 84.0 | + 8.0 (10%) |
| Dorsiflexion | Good | Left | 32.0 | 44.0 | +12.0 (27%) |
| Eversion | Good | Left | 40.0 | 43.0 | + 3.0 (9%) |
| **Case 2:** | | | | | |
| Knee extension | Good | Right | 56.0 | 80.0 | +24.0 (33%) |
| Hip internal rotation | Good | Right | 16.0 | 17.0 | + 1.0 (6%) |
| Hip external rotation | Good | Right | 21.0 | 22.0 | + 1.0 (4%) |
| Knee flexion | Good | Right | 31.0 | 38.0 | + 7.0 (16%) |
| Hip adduction | Good | Right | 50.0 | 52.0 | + 2.0 (4%) |
| Hip abduction | Good | Right | 37.0 | 49.0 | +12.0 (25%) |
| **Case 3:** | | | | | |
| Knee flexion | Good | Left | 40.0 | 40.0 | 0 |
| Knee extension | Good | Left | 72.0 | 92.0 | +20.0 (22%) |
| **Case 4:** | | | | | |
| Foot eversion | Fair | Left | 24.0 | 31.0 | + 7.0 (24%) |
| Foot dorsiflexion | Fair | Left | 18.0 | 21.0 | + 3.0 (14%) |
| Foot dorsiflexion and inversion | Fair | Left | 5.6 | 8.6 | + 3.0 (33%) |
| Knee extension | Good | Left | 64.0 | 76.0 | +12.0 (16.6%) |
| Hip flexion | Good | Left | 45.0 | 54.0 | + 9.0 (14%) |
| Knee flexion | Good | Left | 30.0 | 34.0 | + 4.0 (12.5%) |
| Hip abduction | Good | Left | 68.0 | 68.0 | 0 |
| **Case 5:** | | | | | |
| Elbow flexion | Fair | Left | 15.0 | 16.0 | + 1.0 (6.2%) |
| Elbow flexion | Poor | Right | 31.0 | 31.0 | 0 |
| Knee extension | Good | Right | 42.0 | 46.0 | + 4.0 (9%) |
| Knee extension | Good | Left | 50.0 | 62.0 | +12.0 (20%) |
| Hip flexion | Fair | Left | 19.0 | 22.0 | + 3.0 (14%) |
| Knee flexion | Good | Left | 30.0 | 36.0 | + 6.0 (16.6%) |
| Knee flexion | Good | Right | 28.0 | 34.0 | + 6.0 (17%) |
| Wrist extension | Fair | Left | 5.8 | 5.8 | 0 |
| Wrist extension | Good | Right | 18.5 | 21.0 | + 2.5 (15%) |
| Shoulder extension | Poor | Left | 6.2 | 6.8 | + 0.6 (9%) |
| Shoulder extension | Fair | Right | 6.0 | 13.0 | + 7.0 (50%) |
| Elbow extension | Poor | Right | 4.8 | 5.4 | + 0.6 (11%) |
| **Case 6:** | | | | | |
| Elbow flexion | Poor | Left | 9.8 | 11.0 | + 1.2 (10%) |
| Wrist flexion | Poor | Left | 5.0 | 5.4 | + 0.4 (7.7%) |
| Wrist internal rotation | Fair | Left | 2.8 | 2.6 | − 0.2 (−7.7%) |
| Shoulder flexion | Fair | Left | 4.2 | 5.2 | + 1.0 (20%) |
| Shoulder vertical abduction | Fair | Left | 3.0 | 5.4 | + 2.4 (45%) |
| Shoulder horizontal adduction | Fair | Left | 6.8 | 8.0 | + 1.2 (16%) |
| Shoulder extension | Fair | Left | 2.6 | 3.4 | + 0.8 (24%) |
| **Case 7:** | | | | | |
| Foot dorsiflexion and inversion | Fair | Left | 7.4 | 8.0 | + 0.6 (7.7%) |
| Foot dorsiflexion | Good | Left | 6.6 | 11.0 | + 4.4 (40%) |
| Knee extension | Good | Left | 80.0 | 88.0 | + 8.0 (9%) |
| Hip flexion | Good | Left | 28.0 | 38.0 | +10.0 (24%) |
| Hip extension | Good | Left | 32.0 | 36.0 | + 4.0 (11%) |
| Knee flexion | Fair | Left | 11.0 | 14.0 | + 3.0 (20%) |
| Hip abduction | Poor | Left | 14.0 | 17.0 | + 3.0 (16.6%) |
| **Case 8:** | | | | | |
| Knee extension | Fair | Left | 17.5 | 20.0 | + 2.5 (12.5%) |
| Knee extension | Good | Right | 60.0 | 62.0 | + 2.0 (3.2%) |
| Hip flexion | Good | Right | 20.0 | 24.0 | + 4.0 (16.6%) |
| Hip flexion | Fair | Left | 15.0 | 18.0 | + 3.0 (16.6%) |
| Knee flexion | Good | Left | 19.0 | 22.0 | + 3.0 (14.3%) |
| Knee flexion | Fair | Right | 11.5 | 12.0 | + 0.5 (4%) |
| Elbow extension | Fair | Left | 14.0 | 15.0 | + 1.0 (6.6%) |
| Elbow extension | Good | Right | 26.0 | 30.0 | + 4.0 (14%) |
| Hip abduction | Good | Left | 45.0 | 48.0 | + 3.0 (7.5%) |
| Hip abduction | Fair | Right | 36.0 | 44.0 | + 8.0 (20%) |
| Shoulder flexion | Good | Left | 18.0 | 21.0 | + 3.0 (14%) |
| Shoulder flexion | Fair | Right | 21.0 | 26.0 | + 5.0 (20%) |
| Shoulder vertical abduction | Good | Left | 18.0 | 24.0 | + 6.0 (25%) |
| Shoulder vertical abduction | Good | Right | 18.0 | 22.0 | + 4.0 (19%) |
| Shoulder extension | Fair | Left | 20.0 | 27.0 | + 7.0 (24%) |
| Shoulder extension | Fair | Right | 32.0 | 32.0 | 0 |
| **Case 9:** | | | | | |
| Knee extension | Fair | Left | 20.0 | 20.0 | 0 |
| Hip flexion | Fair | Left | 12.0 | 18.0 | + 6.0 (33%) |
| Hip abduction | Good | Left | 39.0 | 47.0 | + 8.0 (12.5%) |
| Knee flexion | Good | Left | 30.0 | 36.0 | + 6.0 (16.6%) |
| **Case 10:** | | | | | |
| Foot dorsiflexion | Fair | Right | 3.0 | 5.4 | + 2.4 (40%) |
| Foot dorsiflexion | Fair | Left | 2.0 | 5.8 | + 3.8 (62%) |
| Knee extension | Good | Left | 60.0 | 52.0 | − 8.0 (−14%) |
| Knee extension | Good | Right | 44.0 | 41.0 | − 3.0 (−7%) |
| Knee flexion | Good | Left | 30.0 | 33.0 | + 3.0 (9%) |
| Knee flexion | Good | Right | 34.0 | 34.0 | 0 |

*+ = increase; − = decrease.

failed to obtain an increase in any of the 7 muscle actions studied.

No patient demonstrated improvement in all the muscles tested. In Table 3 the number of muscles that increased in strength 20 per cent or more is tabulated against the total number of muscles for each patient tested, and the percentage of muscles with a significant increase is listed. The results were also analyzed to determine if any special muscle groups showed a significant rise as compared with others. Of the 21 muscle actions tested, 9 increased 20 per cent or more, with the following distribution: hip adduction, 2; hip flexion, 3; hip abduction, 2; shoulder flexion, 1; shoulder abduction, 1; shoulder extension, 3; knee extension, 3; knee flexion, 3; and ankle dorsiflexion, 3.

TABLE 3.

| CASE NO. | NO. OF INCREASES | TOTAL NO. OF MUSCLES | PERCENTAGE OF MUSCLES INCREASING IN STRENGTH |
|---|---|---|---|
| 1 | 3 | 9 | 33.3 |
| 2 | 2 | 6 | 33.3 |
| 3 | 1 | 2 | 50.0 |
| 4 | 2 | 7 | 28.0 |
| 5 | 2 | 12 | 16.6 |
| 6 | 0 | 7 | 0 |
| 7 | 3 | 7 | 42.0 |
| 8 | 4 | 16 | 25.0 |
| 9 | 1 | 4 | 25.0 |
| 10 | 2 | 6 | 33.3 |
| Totals | 20 | 76 | |
| Average | | | 26.0 |

The strength of the muscles before medication according to the usual manual testing was graded as poor, fair or good, the number of muscles in each grade being 9, 26 and 41 respectively. No muscles graded as poor, 11 (42 per cent) graded as fair, and 9 (21 per cent) graded as good demonstrated a 20 per cent increase or more.

### *Side Effects*

While under medication most patients believed that there was a slight gain in weight without any noticeable improvement in appetite. Actual measurements showed that all but 2 patients did have a slight increase in weight, the greatest amount being 4 pounds in 2 cases. One patient who had been bothered by cramping of the muscles affected found that this disappeared shortly after he began medication. Another patient, however, who had never previously noticed cramps had them occasionally while on medication. Aside from this, there were no unpleasant side effects; on the other hand, there was no subjective sensation of improvement in muscle power. None of the patients knew the actual numerical results, and none of them felt enough improvement in performance to wish to continue beyond the test period. In fact, 1 patient was anxious to discontinue treatment so that he could resume his progressive-resistance exercises, which he had been doing for two years for selected muscle groups (the only muscles that showed improvement were those that had never been given progressive-resistance exercises).

## DISCUSSION

The general impression obtained from analysis of this study was that no striking improvement in muscle strength was obtained either subjectively or objectively. Although the medication was given internally and one would expect any effect to be a general one on the muscles involved, only 26 per cent of the muscles showed definitely significant increases in strength during a single effort test. It is true, however, that improvement in some of the muscles occurred in 9 out of 10 patients, including the patient who had had infectious polyneuritis. This suggests that the drugs had a real effect on muscle metabolism as demonstrated by ability to perform maximum single contractions. The mechanism of such an effect, however, was not studied, and no theories are offered. In the patient who had had two years of progressive-resistance exercises beginning two years after the onset of the disease, improvement was observed only in muscle groups that had never received the exercises.

The degree of improvement of muscle strength after medication was not great enough or consistent enough to warrant use of placebos during an initial period although this had been planned. Both consistent objective improvement and subjective sense of improvement were lacking, further nullifying the need of control observations in this experimental study.

## SUMMARY AND CONCLUSIONS

Nine patients with residual weakness one or two years after an attack of poliomyelitis and 1 after infectious polyneuritis were studied to determine the effect of betaine and glycocyamine on muscle strength.

Muscle strength was measured by means of standardized testing technics for the break resistance required for a variety of muscle actions as measured in pounds with a calibrated gauge instrument recording strain.

Only 26 per cent of the muscles tested showed as much as a 20 per cent increase in strength, which did not appear significant subjectively or functionally.

When increases in strength occurred they appeared in muscles that had not received intensive exercise to increase power.

Under the conditions of this study betaine and glycocyamine were not considered to have significant value in the treatment of muscle weakness as a residuum of poliomyelitis.

# INTERPRETATION OF THE ONE-STAGE METHOD FOR DETERMINING PROTHROMBIN TIME*

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THE clinical usefulness of the one-stage prothrombin-time method has long been recognized and acknowledged, but opinions concerning the interpretation of the results remain divergent. No general agreement has been reached whether the test can specifically determine the prothrombin concentration of the blood. A study was made to obtain additional data that might aid in evaluating the results of this test. The procedures used in this investigation have been described previously.[1]

TABLE 1. *Prothrombin Time in Normal Subjects and in Patients with Various Types of Hemorrhagic Diseases and Tuberculosis.*

| PROTHROMBIN TIME | | | |
|---|---|---|---|
| NORMAL ADULTS | PATIENTS WITH HEMOPHILIA | PATIENTS WITH PURPURA* | PATIENTS WITH TUBERCULOSIS† |
| sec. | sec. | sec. | sec. |
| 12½ | 12 | 12 | 13 |
| 12 | 12 | 13 | 12 |
| 12 | 13 | 12 | 14 |
| 12 | 12 | 12 | 13 |
| 12 | 12 | 12 | 14 |
| 12 | 12½ | 12½ | 12½ |
| 12 | 13 | 12 | 13 |
| 12 | 12 | 12 | 12 |
| 12 | 12 | 12 | 12 |
| 12 | 12 | 12 | 12 |
| 12 | 12 | 12 | 12 |
| 12 | 11½ | 12 | 12 |

*The first 6 cases were thrombocytopenic purpura. In the remainder, no diminution of platelets occurred.

†The last 4 patients received vitamin K.

## VARIATION OF THE PROTHROMBIN TIME IN MAN

The one-stage method was carried out on several hundred subjects to find the limits of variation in nonhypoprothrombinemic states. As representative samples, the results on 12 normal subjects studied consecutively and on an equal number of patients with hemophilia, purpura and tuberculosis are presented in Table 1. In normal subjects, the prothrombin time rarely exceeds 12½ seconds or decreases below 11½ seconds, provided care is taken in collecting the blood and carrying out the determination promptly.

In an occasional case of purpura and of hemophilia the prothrombin time may be 13 seconds, but rarely longer. This is often corrected with a small dose of vitamin K. In tuberculosis a mild hypoprothrombinemia has been repeatedly reported, an observation that was borne out in the present study. Since the prothrombin time can readily be brought to normal with vitamin K, it seems likely that a slight inadequacy of vitamin K is not uncommon in a chronic infectious disease such as tuberculosis. Whether this is the result of an induced defective absorption of vitamin K from the intestine or to an increased metabolic demand for vitamin K, not quite met by the amount available from the diet, remains to be determined. Since recent studies in this laboratory indicate that the amount of natural vitamin $K_1$ absorbed even under normal conditions is small,[2] the second explanation seems the more probable.

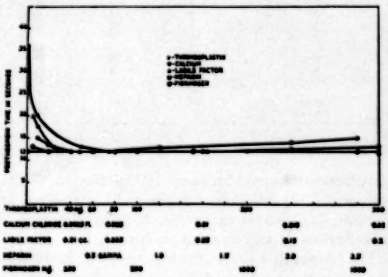

FIGURE 1. *Influence of the Concentration of Various Factors on the Prothrombin Time.*

*The standard procedure consisted in the addition of 0.1 cc. of calcium chloride to 0.1 cc. of thromboplastin and 0.1 cc. of oxalated plasma. The concentration given is as follows:*

*Thromboplastin: the quantity of acetone-dehydrated rabbit brain extracted with 5 cc. of saline solution.*

*Calcium chloride: the concentration employed in the test.*

*Labile factor: the quantity of fresh deprothrombinized rabbit plasma added to 1 cc. of plasma.*

*Heparin: the quantity added to 1 cc. of plasma.*

*Fibrinogen: the quantity in 100 cc. of plasma.*

The normal prothrombin time observed in hemophilia and in various forms of purpura, including the thrombocytopenic and nonthrombocytopenic types, is important in differential diagnosis. The occasional, mild hypoprothrombinemia justifies the administration of vitamin K in such cases. Although the basic defect is uninfluenced, the correction of even a mild hypoprothrombinemia may be beneficial since such a condition superimposed upon a primary disturbance of hemostasis is apt to accentuate the bleeding state.

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### Variables in the Prothrombin Time

According to the classic theory of coagulation, thromboplastin, calcium and prothrombin interact to form thrombin. Mertz and his associates[3] showed that this reaction is stoichiometric. With the discovery of the labile factor in 1943,[4] the clotting theory had to be revised. As a guide, the formation of thrombin may be expressed by the equation:

Thromboplastin + labile factor + calcium + prothrombin = thrombin.

Other factors participating in this reaction have been postulated, but discussion of these is postponed, to present clearly the effect of variations of the known agents on the prothrombin time.

Figure 1 shows the effect of the concentration of the known agents needed to form thrombin as well as of fibrinogen and heparin on the prothrombin time. A lack of thromboplastin, labile factor, fibrinogen or calcium causes a prolonged prothrombin time. As each of these is increased the prothrombin time decreases until 12 seconds is attained, after which no further change occurs except for calcium, a rise in the concentration of which increases the prothrombin time, showing that excess calcium has an inhibitory action.

On the assumption that the factors presented in Figure 1 constitute the essential constituents needed to form thrombin, it can be concluded that the prothrombin time is a function of the prothrombin concentration provided the calcium concentration is optimum and the thromboplastin, labile factor and fibrinogen are above a minimum required level. A concentration of heparin below 1 gamma per cubic centimeter of plasma has no significant influence. It is important to note that an excess of labile factor does not shorten the prothrombin time to less than 12 seconds provided that the plasma is fresh and has not been in contact with glass. It therefore seems incorrect to consider the labile factor to be an accelerator. Such names as acglobulin (accelerator globulin) and proaccelerin, which are considered synonymous with labile factor, are consequently apt to be misleading.

### Changes in Prothrombin Activity in Vitro

When 9 vol. of human blood is mixed with 1 vol. of either 0.1 M (one-tenth molar) sodium oxalate or 0.2 M sodium citrate solution, the resulting plasma will, when stored at 4°C., show a progressive increase in prothrombin time (Table 2). The change in the sample stored in the silicone-coated test tube is apt to be somewhat more pronounced than that of a sample kept in glass. If 0.1 M sodium citrate is used, the prothrombin time of plasma stored in a silicone tube shows little change, whereas the sample in contact with glass has a shorter time than the fresh plasma. The increase of prothrombin time can be satisfactorily explained by the loss of the labile factor. The early observation that the stability of the labile factor is decreased by the removal of calcium[4] partly explains why the decrease is slower when 0.1 M sodium citrate is used since this concentration does not entirely depress the calcium ions.[5]

Since rabbit plasma is rich in labile factor and since the agent is not removed by tri-calcium phosphate, which quantitatively absorbs prothrombin, fresh oxalated rabbit plasma thus deprothrombinized serves as a simple but reliable means for restoring labile factor. When a small amount of this plasma is added to the samples of stored plasmas kept in silicone-coated test tubes, the prothrombin time becomes 12 seconds but decreases to 8 or 9 seconds for plasma in glass. It is obvious that during storage in glass something greatly increases prothrombin activity above that of fresh plasma. Owing to the loss of labile factor, this augmented activity is masked in decalcified plasma. In the sample with 0.1 M sodium citrate, enough labile factor remains to show this increase even without the addition of extra labile factor. It is clear that contact with glass brings about an increased prothrombin activity in human plasma. The importance of this when one is interpreting the prothrombin time as a measure of prothrombin is evident. The two most likely explanations are as follows: either an actual increase in prothrombin occurs, or a factor is generated that speeds the con-

Table 2. *Changes in the Prothrombin Activity of Plasma During Storage.*

| Anticoagulant | Surface of Container | Prothrombin Time at 0 Hr. | Prothrombin Time at 0 Hr. Labile Factor Added[a] | Prothrombin Time at 24 Hr. | Prothrombin Time at 24 Hr. Labile Factor Added | Prothrombin Time at 48 Hr. | Prothrombin Time at 48 Hr. Labile Factor Added |
|---|---|---|---|---|---|---|---|
| | | sec. | sec. | sec. | sec. | sec. | sec. |
| 0.1 M. sodium oxalate | Glass | 12 | 12 | 16 | 9 | 20 | 8½ |
| | Silicone | 12 | 12 | 18 | 11½ | 22 | 12 |
| 0.2 M sodium citrate | Glass | 12 | 12 | 13 | 9 | 13½ | 9 |
| | Silicone | 12 | 12 | 15 | 11½ | 15½ | 12 |
| 0.1 M. sodium citrate | Glass | 12 | 12 | 9 | 7½ | 9½ | 8 |
| | Silicone | 12 | 12 | 12 | 11½ | 12 | 11½ |

[a]One volume of deprothrombinized rabbit plasma was added to 9 vol. of the stored plasma.

version of prothrombin to thrombin. The latter explanation is expounded especially by Alexander[6] who has proposed the name serum prothrombin converting accelerator (S.P.C.A.). The proconvertin of Owren[7] and Factor VII of Koller[8] are likewise offered as explanations of the changes of prothrombin activity observed in vitro.

The evidence that has led to the conclusion that an actual increase of prothrombin occurs when human blood is stored in glass has been presented in a series of papers.[9-11] It has been postulated that in adult human blood the prothrombin exists partly in an inactive state, prothrombinogen, and partly as active prothrombin. According to this concept, the one-stage method measures only active prothrombin. When all the prothrombin in normal adult blood is converted to the free state, the prothrombin time becomes 8 seconds. This conversion is hastened by contact with glass. On storage at 4°C. the activation of prothrombinogen requires

TABLE 3. *Prothrombin Time in the Newborn Infant and in the Mother.*

| SUBJECT | PROTHROMBIN TIME | TOTAL PROTHROMBIN TIME* | REMARKS |
|---|---|---|---|
| | sec. | sec. | |
| Mother .... | 14 | 8¼ | No vitamin K given |
| Baby ..... | 15¼ | 15 | |
| Mother .... | 13½ | 8½ | No vitamin K given |
| Baby ..... | 15 | 15 | |
| Mother .... | 12 | 8¼ | Vitamin K given before birth |
| Baby ..... | 12 | 12½ | |
| Mother .... | 11¾ | 8½ | Vitamin K given before birth |
| Baby ..... | 12 | 13 | |

*Prothrombin time after 48 hours' storage with added labile factor.

twenty-four hours or more. When human plasma depleted of platelets or low in thromboplastinogen, as in severe hemophilia, is clotted in glass at 37°C. the serum promptly acquires a prothrombin time of 8 or 9 seconds. This suggests that a rapid activation of prothrombinogen occurs under these conditions, and since little thromboplastin is available, nearly all the prothrombin remains unconsumed. The serum consequently contains more active prothrombin than the plasma, which accounts for its shorter prothrombin time. The recognition that the alteration in prothrombin activity observed in vitro may be brought about by factors different from those that operate in vivo to change the prothrombin time makes it desirable to reconsider the hypoprothrombinemia seen in newborn infants and in patients receiving Dicumarol.

## HYPOPROTHROMBINEMIA OF THE NEWBORN INFANT

Soon after the development of the two prothrombin methods, it was established that a newborn baby supplied with vitamin K had a normal prothrombin time, but a prothrombin concentration of only a fourth to a third of that found in adult blood estimated by the two-stage method of Brinkhous, Smith and Warner.[12] Since no satisfactory explanation could be offered for these differences, a further study was recently undertaken. It was found that when the mother was supplied with vitamin K in addition to the amount in her diet, the prothrombin time of both maternal and infant blood was 12 seconds.[13] Significantly, however, when the oxalated plasma was stored and the prothrombin time determined after readdition of labile factor, the blood of the mother had a prothrombin time of 8 or 9 seconds, but infant or umbilical-cord blood was 12 seconds. When no extra vitamin K was given, the prothrombin time of the cord blood as well as of the infant's blood immediately after birth was prolonged. On storage, the prothrombin time corrected by the addition of labile factor remained the same as that of the fresh blood. The prothrombin time of the mothers' blood, on the contrary, even when slightly prolonged, developed the normal shortening to 8 or 9 seconds on storage (Table 3).

According to the concept that prothrombin may exist in an active or an inactive state, a simple explanation can be given for the differences between the babies' and the mothers' bloods. The baby supplied with an adequate quantity of vitamin K has a normal prothrombin time, which means that the concentration of free prothrombin is the same as that in adult blood. Since no increase in prothrombin activity occurs when umbilical-cord or infant blood is stored, one may conclude that no prothrombinogen is present. The infant apparently lacks the power to form this inactive prothrombin. The total prothrombin, therefore, is the same as the free prothrombin time. Since the latter fraction constitutes only about a fourth of the total in adult human blood, the total prothrombin of the baby is only approximately 25 per cent of the total present in older children and adults. This agrees with the results obtained by means of the two-stage method, which is to be expected. Because of the various manipulations required in the two-stage test, all the prothrombinogen becomes activated, and the procedure therefore estimates total prothrombin.

The alternative explanation, that an accelerator accounts for the normal prothrombin time in the baby's blood when the prothrombin as measured by the two-stage method is only a fourth of normal, requires one to assume that the marked reduction of prothrombin is so perfectly counterbalanced by an excess of accelerator that a prothrombin time of exactly 12 seconds results. It is an unusual coincidence that a compensatory mechanism should be so quantitatively exact. This becomes even more extraordinary when one considers that the hypoprothrombinemia in the baby's blood is promptly corrected by vitamin K to 12 seconds but the total prothrombin fails to be elevated above 30 per cent.

The theory that a compensatory accelerator explains the normal prothrombin time in the new-

born infant becomes entirely confusing because of the recent report of Loeliger and Koller[14] that Factor VII is markedly decreased in umbilical-cord blood. If their factor is the same as the proconvertin of Owren and S.P.C.A. of Alexander, it must be concluded that such a factor has no influence on the one-stage prothrombin time because it is normal in the newborn baby when the mother receives vitamin K.

### Hypoprothrombinemia Due to Dicumarol

When Dicumarol is given to either man or animals, the prothrombin time increases, and the prothrombin as measured by the two-stage method is decreased. This makes it appear highly probable that an actual diminution of prothrombin occurs. Recently, it was found that in dogs the hypoprothrombinemia induced by Dicumarol is indistinguishable from that caused by vitamin K deficiency.[15] If it is assumed that lack of vitamin K specifically causes a decrease of prothrombin, it may be concluded that in the dog, Dicumarol likewise reduces only prothrombin.

In man the results of the two-stage method correspond fairly well with the prothrombin time in estimations of the prothrombin level after Dicumarol, but in certain cases marked discrepancies have been reported. According to the accelerator-factor theory, Dicumarol reduces not only prothrombin but also the converting factor. A recent study on a series of patients gave results that, when interpreted in accordance with the prothrombinogen theory, showed that Dicumarol lowers both the total and the free prothrombin and that a rough ratio is maintained between the two forms.[16]

The following findings resulting from severe poisoning with Dicumarol offer an interesting problem of interpretation:

| | |
|---|---|
| Clotting time (Lee–White method) | No clot |
| Prothrombin time | 540 seconds |
| Total prothrombin time | 37 seconds |
| Labile factor | Normal (method of Quick[1]) |
| Prothrombin time after administration of vitamin $K_1$ oxide | 37 seconds in 8½ hours<br>16 seconds in 16 hours |

According to the prothrombinogen theory, the findings suggest that the total prothrombin — that is, the prothrombin time obtained after the plasma had been stored in glass and excess labile factor added — was still sufficient to give a value of 37 seconds. The labile factor, it should be noted, remained normal and therefore exerted no influence on the marked decrease of prothrombin activity. When the prothrombin-converting accelerator hypothesis is applied to explain the findings, it would be concluded that although the prothrombin was reduced, it still could produce clotting in 37 seconds, and, therefore, the markedly prolonged prothrombin time of 540 seconds was caused mainly by a lack of the accelerator. Since vitamin $K_1$ oxide rapidly improved the prothrombin time, it follows, according to this explanation, that vitamin K is concerned mainly with the production of the accelerator factor. This assigns to vitamin K a function that overshadows in importance its role in producing prothrombin.

### Discussion

The importance of the prothrombin time in clinical practice makes it desirable to know what the test means. A dispassionate analysis of the known facts may not give the complete answer, but it can dispel some of the confusion. Whether the prothrombin time determines specifically active prothrombin or whether it estimates the composite effect of prothrombin and a conversion accelerator cannot be conclusively decided on the experimental evidence thus far obtained, although the concept of an inactive prothrombin offers what appear to be a more simple and practical explanation. It is of more immediate importance to know whether this test, when carried out on fresh, undiluted plasma, furnishes results that express the physiologic state better than other tests designed to measure prothrombin activity. It is well established that when the prothrombin time of the blood of the newborn baby is 12 seconds, the baby is in no more danger of hemorrhage than a normal adult even though its prothrombin as measured by the two-stage method is one third or less of normal. In cholemic bleeding the test has been equally reliable.

Although the method is being used extensively in controlling Dicumarol therapy, occasional claims are made that it is unreliable. One investigator[17] makes the following serious charge: "Because of the several uncontrolled factors other than prothrombin, the one-stage method test has led to errors in prothrombin estimation and may have been responsible for fatal hemorrhages from the use of Dicumarol." It is unfortunate that when such incidents occur, the details are not reported so that one might know why and how the test has failed.

To judge the one-stage method equitably, strict adherence to details is necessary. A thromboplastin that yields variations of several seconds in normal plasmas is unreliable, since it has repeatedly been shown that the prothrombin in normal subjects is remarkably constant. It is essential to emphasize the fact that blood in contact with glass becomes altered and that such changes affect the prothrombin time. One must therefore distinguish sharply between the intrinsic prothrombin time from one that results from contact with glass and the addition of various agents other than thromboplastin.

## Summary

The prothrombin time when determined by the standardized one-stage procedure is constant in normal subjects. Changes in the prothrombin time may be intrinsic (from physiologic causes) or extrinsic — that is, induced by the environment of the blood after it has been drawn.

It is postulated that in man part of the prothrombin exists in an inactive form, prothrombinogen, and part as free or active prothrombin. It is only the latter fraction that is measured by the unmodified one-stage procedure.

When oxalated human plasma is stored, labile factor disappears, resulting in a prolonging of the prothrombin time. Simultaneously, prothrombinogen is converted to free prothrombin, presumably by the catalytic action of a glass surface. The lack of labile factor masks the increased prothrombin activity in the stored plasma, but resupplying of labile factor causes an increase in activity.

The application of the concept of an active and an inactive prothrombin to the hypoprothrombinemia from Dicumarol and in the newborn infant is discussed and compared with the theory of a prothrombin accelerator.


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# RENAL THROMBOSIS COMPLICATING EPIDEMIC DIARRHEA OF THE NEWBORN*

## Nephrectomy with Recovery


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RENAL thrombosis may be defined as an acute occlusive phenomenon involving the renal venous system, totally or in part, and resulting in a hemorrhagic destruction and loss of function of the parenchymatous tissue. The condition usually occurs between birth and six months of age, although a case in a patient three years of age has been reported.[1] The sexes are equally involved, and the majority of cases are associated with dehydration and sepsis. The disease most frequently complicated by renal thrombosis is acute ileocolitis, particularly epidemic diarrhea of the newborn.

The case reported below occurred in 1 of 10 infants in a nursery for the newborn simultaneously afflicted with severe diarrheal disease in the first few days of life. It was of particular interest that the infants in this group had evidence of renal involvement in addition to the usual signs and symptoms associated with epidemic diarrhea. Gross hematuria was recorded in but 1 case; however, red and white blood cells, granular casts and large amounts of albumin were present in the urinary sediment on several examinations over a period of one to three weeks in each of the other patients.

There were 3 deaths in this series. An autopsy examination was performed on 1 infant in whom both kidneys were found to be markedly enlarged, measuring 8 by 6 cm., and involved in a hemorrhagic infarction associated with thromboses within the renal veins.

Six of the infants who survived this epidemic were ill for an average of three weeks and recovered completely after vigorous medical management. None of these children had abdominal masses during the acute illness or convalescence. Clinical improvement was closely correlated with the clearing of abnormal urinary findings.

The remaining survivor was admitted to the Children's Hospital on the seventh day of his illness and a left nephrectomy for renal-vein thrombosis was subsequently performed.


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## Case Report

R. T. (C. H. 5190908), a 7-day-old male infant, was admitted to the hospital on November 22, 1951, because of diarrhea, cyanosis and dehydration. The pregnancy, delivery and progress had been normal until the 3d day of life, when he began to pass frequent watery yellow stools. He had been discharged from the community hospital at the age of 5 days. At home the stools increased in frequency, and he was placed on a skimmed-milk formula, without improvement. On the morning of the day of admission, he appeared severely dehydrated, and tachypnea and cyanosis developed. A hypodermoclysis of glucose in saline solution was administered in the home, and he was taken to the hospital, where he arrived in a state of shock. There was no history of pyrexia, rash, vomiting, melena or hematuria.

At the time of admission, the child was acutely ill, breathing rapidly and deeply, and exhibiting definite circumoral pallor and generalized mottled cyanosis. The abdomen was soft; the liver edge was palpated 1½ fingerbreadths below the right costal margin, and the spleen was palpable 1 fingerbreadth below the left costal margin.

The temperature was 98°F., the pulse 150, and the respirations 40.

Blood and stool cultures were performed, and intravenous infusions of fluid and electrolyte, including plasma, were initiated. Examination of the blood showed a hemoglobin of 15.9 gm. per 100 cc. and a white-cell count of 11,000, with 56 per cent neutrophils. The first urine specimen, obtained 6 hours after admission, was cloudy yellow and acidic in reaction, with 200 mg. of albumin per 100 cc.; the sediment contained 1 or 2 white cells and 4 or 5 finely and coarsely granular casts per high-power field.

Intravenous infusions of sodium sulfadiazine, 0.5 gm. (8 gr.) a day, and intramuscular injections of penicillin were started and continued for 3 days. The infant's general condition improved. The temperature rose to 101.4°F. 12 hours after admission, and the stools decreased rapidly in number and became formed within 36 hours, when oral feedings of 5 per cent glucose and water with potassium chloride added were started.

By the 3d hospital day, the temperature was normal, and milk feedings were started. Chemotherapy was discontinued because of the development of a generalized maculoerythematous rash. Despite this clinical improvement, urinalysis revealed the presence of 40 to 50 white cells, 0 to 3 red cells and an occasional granular cast per high-power field and 10 to 120 mg. of albumin per 100 cc. The white-cell count remained elevated, ranging between 12,000 and 15,000. On the 6th hospital day, the 5 strains of *Escherichia coli* from the initial stool culture were identified* as Type 0 111, B4, an antigenic type previously shown to be associated with epidemic diarrhea of the newborn.[2] Disk sensitivities determined with these organisms showed moderate sensitivity to chloramphenicol, which was started in amounts of 25 mg. per kilogram of body weight a day. On this therapy, the stools increased to 6 to 10 per day and became green and watery. The patient again required supplementary intravenous therapy. On the 8th hospital day, a mass in the left flank was noted. This mass produced a visible bulge in the loin, extended down to the iliac crest, was firmly fixed and did not move with respirations. An intravenous pyelogram revealed a normally functioning right kidney and ureter, but no dye was visualized on the left side in the area of an enlarged kidney. On the 13th hospital day, a stool culture showed that *Esch. coli* of different antigenic composition had entirely replaced the pathogenic Type 0 111, B4.

By the 19th hospital day, the renal mass had diminished in size somewhat and had become more discrete. With the preoperative diagnosis of secondarily infected hydronephrotic or infarcted kidney, exploration was carried out. The perirenal fat was hemorrhagic and edematous; the kidney was large, tense and purple. As the perinephric tissues were dissected away, dark, viscid blood oozed from the capsular vessels, suggesting that the primary lesion was venous obstruction. The renal pelvis appeared normal, and the adrenal gland, although slightly hemorrhagic, was not swollen or livid. The ureter, renal arteries and vein were individually ligated, and the kidney was removed.

Oral formula feedings were instituted on the day after operation, and chloramphenicol was administered for the ensuing 5 days. The patient had 2 to 4 yellow stools per day.

On the 6th postoperative day the patient was discharged gaining weight for the first time on oral feedings. The white-cell count was 10,200, and the blood urea nitrogen 9.35 mg. per 100 cc. Urinalysis showed no albumin, with rare white cells, no red cells and no casts in the sediment.

On pathological examination, the removed kidney measured 6 by 4 by 3 cm. and was reddish purple, and when it was cut, dark blood exuded from the tense mottled hemorrhagic surface. The gross architecture was preserved. Microscopical

*Culture performed by Dr. W. W. Ferguson, of the Michigan Department of Health.

A B

Figure 1. *Left Kidney Removed from a Twenty-Six-Day-Old Infant with Unilateral Renal-Vein Thrombosis. The gross architecture is preserved* (A). *The renal vein is completely occluded by an organizing thrombus, and there is hemorrhagic necrosis of the parenchyma, with several small areas of secondary infection* (B).

sections through the hilus of the kidney demonstrated thrombosis of the renal vein in which fibroblastic organization and some recanalization were present. Sections of kidney parenchyma showed hemorrhagic necrosis chiefly involving the pyramids, with streaky involvement of the cortex. Leukocytic infiltration was observed around these necrotic areas (Fig. 1). The final diagnosis was thrombosis of the renal vein with secondary hemorrhagic necrosis and infection.

## Discussion

Renal thrombosis is but one of the severe intravascular complications frequently seen in infants at autopsy. The vessels most commonly involved are the cranial sinuses, renal veins and tributaries of the portal system. Thrombosis of the renal veins is usually bilateral, but it may be unilateral. It may occur in any of the subdivisions of the renal vein and thus result in a localized segmental necrosis or a total infarction of the entire renal parenchyma. Zuelzer et al.,[1] after careful study, have compiled a useful pathological classification of massive degenerative renal diseases of infancy. All gradations of parenchymatous damage from localized areas of intraglomerular occlusion to total bilateral renal-vein thrombosis are included.

The exact cause of the intravenous coagulation is unknown. Stasis of the blood resulting from decreased blood volume, hemoconcentration and arteriolar constriction undoubtedly produces local ischemia and anoxia.

It is also possible that in certain cases of epidemic diarrhea the particular *Esch. coli* antigens 0 111 and, perhaps more probably, the envelope antigen, $B_4$, which bestow the "pathogenic" properties on this type of organism,[2, 3] act as additional damaging agents. The resultant effect of these antigens and the local tissue anoxia is intimal damage of a sufficient degree to provide a nidus for the accumulation of platelets, which upon disintegrating release the tissue substances necessary for the initiation of clot formation. This concept is in agreement with the clinical observations that renal thrombosis rarely occurs in infants except as an accompaniment of epidemic diarrhea of the newborn.[1, 4-9]

The occurrence of secondary infection in an infarcted kidney is uncommon but was reported in 1 of the 2 cases of Campbell and Matthews.[5] The necrosed tissue provides an adequate medium for the propagation of the offending micro-organisms, and the local interference with the circulation makes it difficult to achieve therapeutic effect with antibiotics and chemotherapeutic agents.

Since the ante-mortem diagnosis of renal-vein thrombosis is seldom made, it should be emphasized that gross hematuria is not necessarily present. It was observed in only 1 of 5 cases reported by Fallon,[6] 2 of 14 described by Morison,[8] and 1 of the 2 cases presented by Campbell and Matthews.[5] On the other hand, the development of a mass in the region of one or both kidneys is highly suggestive of the presence of renal-vein thrombosis. In such cases, intravenous pyelograms may be most helpful, since it is possible to determine the presence or absence of normal renal function as well as to delineate large extrarenal masses that may simulate enlargement of the kidney itself. In the case reported above, there was no evidence of function on the involved left side, and the right kidney appeared entirely normal. In the differential diagnosis we therefore considered only the renal lesions that would produce a nonfunctioning mass such as polycystic kidney, multicystic kidney, hydronephrosis and renal infarction.

The results of removal of a unilaterally infarcted kidney have been very satisfactory.[5, 9, 10] The case presented above was no exception, and the subsequent progress of this infant has been entirely normal.

## Summary and Conclusions

A case of unilateral renal-vein thrombosis as a complication of epidemic diarrhea of the newborn due to *Escherichia coli*, Type 0 111, $B_4$, is presented.

This diagnosis is rarely made but should be suspected even in the absence of gross hematuria in any infant with infection and dehydration in whom a mass in the renal area associated with changes in the urinary sediment develops. The surgical removal of the infarcted parenchymatous tissue is indicated provided the other kidney can be demonstrated to be present and functioning satisfactorily.

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# PLANTAR WARTS*

## Cure by Injection

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INJECTION of plantar warts with 1 per cent novocain relieved symptoms in 95 per cent of cases and cured the warts in 73 per cent of cases in a series of 48 patients with this common and painful malady. The simplicity and ease with which the treatment can be given and the absence of disability and pain recommend this method. All treatments are given on an outpatient basis except in an occasional severe case with multiple warts.

The idea for this simple and effective treatment was suggested by an accidental observation made by a surgical technician,§ who, having been approached by a soldier with a plantar wart and a desire to march in a special parade, injected the wart with novocain as a temporary expedient. The soldier marched successfully in the parade; in a few days the plantar wart disappeared. As a result of this observation, the method was successfully applied to this series of patients. A preliminary report was made in March, 1951.[1]

It has been possible to follow 30 of these 48 patients for six months. Of these 30 patients, 22 were cured. In 7 cases a plantar wart was still present but was asymptomatic. Only 1 patient demonstrated no improvement after three injections; in this case the wart was successfully excised. Three patients in the series had extensive plantar warts of the mosaic type and were cured. One of these had approximately 30 warts involving the entire plantar surface of the left foot, and treatment by any of the currently accepted methods would have been extremely difficult.

### METHOD

The treatment consists of the injection of 2 or 3 cc. of 1 per cent novocain under pressure into the base of the wart in the stratum germinativum layer of the epidermis. Best results are obtained with the use of a 26-gauge needle and a Luer Lock dental syringe for injection under pressure. Figure 1 shows the proper technic in cross section. Two important points should be observed: the needle should penetrate to the stratum germinativum through normal skin at the side of the wart; and only one needle puncture should be made because the injected fluid escapes through multiple holes and sufficient pressure cannot be obtained. If the needle is properly placed, there is considerable resistance to injection, and the desired marked blanching of the skin and elevation of the wart will result. If the needle is too deep, there is little resistance to injection and no blanching and elevation of the skin, and no cure will result.

Patients usually become symptom free within twenty-four hours. In five to seven days the wart becomes soft and darkened. Usually, it can be lifted out with a thumb forceps after a week, provided that the injection has been properly made. In a few cases one or two subsequent injections may be necessary, but in the meantime the patient is generally free from pain.

FIGURE 1. *Cross Section of a Plantar Wart, Showing the Needle for Injection at the Proper Depth and Entering the Wart at a Correct Angle for Best Results.*

Follow-up care includes, of course, correction of any chronic foot infections, cleanliness in patients with hyperhidrosis and use of a well fitted plantar arch support in patients with the wart under the metartarsal heads.

### CURRENT PROCEDURES

Popular methods in the treatment of plantar warts include curettage, with electric fulguration of the base,[2] radiation with x-rays or radium[3] and surgical excision followed by skin graft if necessary.[4] All three methods result in varying degrees of success, but they are attended with discomfort, hospitalization, loss of workdays and disability. Warts treated surgically are especially prone to recurrence.

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Painful scars over weight-bearing surfaces frequently occur after operation. Radiation treatment is fraught with danger and poor results unless expertly administered.[5] No one of the three methods is suitable for multiple warts.

### Discussion

The novocain injection of plantar warts appears to be a simple and effective addition to the therapy of this condition without hospitalization and operation and without discomfort and disability to the patient. The explanation for the success of the method is not clear; perhaps cure results from ischemic necrosis of the wart. Certainly, good results do not occur unless marked blanching of the wart in addition to the elevation of the wart itself from the injection is obtained. Novocain of itself has no therapeutic value, but is used because other agents, such as saline solution, cause considerable pain from pressure for several hours after injection.


### Summary

Intracutaneous injection of plantar warts with 1 per cent novocain has proved to be a simple and effective treatment, giving 96 per cent relief of symptoms and 73 per cent absolute cure in a recent series of 48 patients.

The treatment is painless and nondisabling and does not require hospitalization, and results compare favorably with those obtained by current methods of excision, radiation and fulguration.

It is especially adaptable to cases with multiple warts of mosaic type, in which excision or fulguration would be quite disabling.


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# MEDICAL PROGRESS

## PHARMACOLOGIC ASPECTS OF ADRENOCORTICAL STEROIDS AND ACTH IN MAN (Concluded)*


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### CLINICAL USES OF ACTH, CORTISONE AND HYDROCORTISONE

#### Specific Replacement Therapy

##### *Primary Adrenal Insufficiency*

The use of cortisone has greatly improved the effectiveness of replacement therapy in patients with Addison's disease.[47] Although treatment with desoxycorticosterone unquestionably prolonged the life of many of these patients, cortisone has corrected important metabolic defects not affected by desoxycorticosterone: the facilitation of gluconeogenesis, the restoration of water metabolism to normal and the correction of the electroencephalographic abnormalities of Addison's disease. Appetite, muscular strength and work tolerance are improved, and anemia is diminished. These changes, in conjunction with the remarkable sense of well-being imparted by cortisone, have greatly increased the capacity of these patients to withstand the demands of an active, comparatively normal existence.

For maintenance therapy cortisone is administered by mouth in a dose of 12.5 to 25 mg. per day. Because of the frequent occurrence of mental stimulation during the early weeks of treatment, it may be necessary to employ the smaller dose at first. In the occasional patient who is overstimulated by even minute doses of cortisone acetate, hydrocortisone is often well tolerated at a dosage level of 12.5 to 25 mg. per day. The concurrent administration of desoxycorticosterone is deemed essential for the majority of these patients.


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Although the oral administration of cortisone is preferred because of its obvious convenience, intramuscular injection is satisfactory and may be imperative during periods of acute gastrointestinal disturbance. During periods of intercurrent infection or other stress the dosage of cortisone should be elevated temporarily to a level of 50 to 100 mg. per day to meet the increased hormone requirement.

Patients with Addison's disease and active tuberculosis present a special therapeutic problem and provide the one situation in which cortisone therapy in the presence of active tuberculosis can be considered justified at this time. The use of complete substitution therapy, including cortisone in doses of 12.5 to 25 mg. per day, has had no deleterious effects on the tuberculous process. Indeed, the over-all physical and psychic status of these patients has been materially improved.

Classic adrenal crisis has become increasingly uncommon since the advent of cortisone for routine replacement therapy. Since the primary requirement of these patients is an immediate elevation of adrenocortical hormone in the blood and tissues, the intravenous administration of hydrocortisone or cortisone is the procedure of choice. An initial rapid intravenous injection of 50 mg. of hormone followed by a continued intravenous infusion at a rate of approximately 10 mg. per hour produces a prompt and effective therapeutic response. In the presence of marked dehydration and hypotension moderate doses of desoxycorticosterone acetate in oil (5 to 10 mg. on the first day and 2.5 to 5 mg. daily thereafter) should also be administered.

The availability of cortisone has made complete bilateral adrenalectomy possible in treatment of hypertension and neoplastic diseases. The following program has proved eminently successful for the support of patients during operation:

Cortisone, 100 mg. intramuscularly, twelve and two hours before operation.

Hydrocortisone (or cortisone), 10 mg. per hour intravenously, during and four to six hours after operation.

Cortisone, 50 mg. intramuscularly, every six hours on the first postoperative day.

Cortisone, 50 mg. intramuscularly, every eight hours, on the second and third postoperative days, and every twelve hours, on the fourth and fifth postoperative days.

Cortisone, 25 mg. by mouth, every six hours on the sixth postoperative day and thereafter gradually reduced to maintenance levels of 12.5 to 25 mg. twice daily.

Maintenance of the adrenalectomized patient is, in general, similar to that of the patient with spontaneous primary adrenal insufficiency. The majority of patients can be successfully maintained on a regimen consisting of 37.5 to 50 mg. of cortisone per day in addition to 3 to 6 gm. of supplementary sodium chloride. This program is especially desirable for patients who have undergone adrenalectomy because of hypertensive cardiovascular disease since, on theoretical grounds, the use of desoxycorticosterone is undesirable. On the other hand, in normotensive patients with metastatic carcinoma of the prostate or breast the use of desoxycorticosterone is often advisable although the requirement of some of these patients is considerably less than that of most patients with Addison's disease.

*Secondary Adrenal Insufficiency*

Since adrenocortical hypofunction may be an important consequence of anterior pituitary failure, stimulation with ACTH appears to offer the physiologically ideal type of substitution therapy. Experience to date, however, has been relatively unsatisfactory because of the need for daily injections of hormone and the development of ACTH "resistance."[509] The simplicity and effectiveness of cortisone by mouth makes it at present the treatment of choice in secondary, as well as primary, adrenal insufficiency. The dosage is identical with that described for the primary type. Desoxycorticosterone should be administered to patients who are incapable of maintaining adequate electrolyte balance on cortisone alone, and testosterone and thyroid are given as indicated.

## Diagnostic Use

*Adrenocortical Insufficiency*

ACTH has been used as a diagnostic agent in the evaluation of adrenocortical function since it provides a comparatively simple and specific test of the capacity of the adrenal cortex to respond to its natural activator.[48, 481] The accuracy of the procedure depends upon the validity of the indexes employed, the simplest of which is the change produced in the level of circulating eosinophils. Whereas a significant eosinopenia after the administration of ACTH is a reliable index of adrenal activation, it should be emphasized that the level of blood eosinophils may fall in response to other pharmacologic agents or to stress, without necessarily involving a detectable increase in the rate of adrenal-hormone secretion.[3] Therefore we recommend that *in the final evaluation of adrenocortical function changes in the excretion of urinary steroids should be measured in addition to changes in circulating eosinophils.*

The most convenient "screening" test consists of measuring the change in circulating eosinophils four hours after the intramuscular injection of 25 *U.S.P.* units of a lyophilized ACTH preparation. A fall of 50 per cent or more constitutes a normal response. It is apparent that an adequate number of eosinophils must be present before changes in the cell count can be considered statistically reliable,[509] that the eosinophil fall produced must exceed that due to normal diurnal variation[401] and

that the ACTH preparations used must be potent. Furthermore, this test should not serve as the sole criterion of the state of adrenocortical responsiveness.

For a more critical evaluation of adrenocortical reserve, a vigorous and more prolonged adrenal stimulation must be employed. Two alternative procedures are currently used. The first is continuous intravenous infusion of 20 to 25 units of ACTH during an eight-hour period on two consecutive days.[602] In this test a normal response consists of an 85 to 100 per cent fall in eosinophils and a significant increase in the urinary output of 17-hydroxycorticoids[79] (average normal rise, 10 mg. per twenty-four hours on the first day and 20 mg. per twenty-four hours on the second ) and 17-ketosteroids (average normal rise, 4.4 mg. per twenty-four hours on the first day and 8.7 mg. per twenty-four hours on the second). The other is

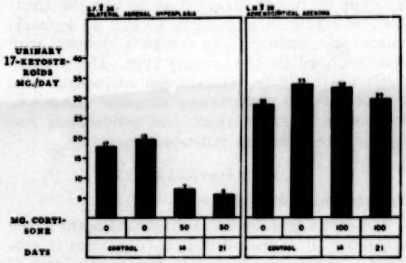


FIGURE 29. *Adrenal Inhibition with Daily Intramuscular Injection of Cortisone (Tumor vs. Hyperplasia).*

intramuscular injection of ACTH gel at a dosage level of 60 to 80 clinical units daily on two consecutive days. The responses produced are comparable to those achieved after the intravenous test previously described.

The adrenocortical response to ACTH in patients with adrenocortical insufficiency secondary to pituitary failure is variable, depending on the extent and duration of atrophy. In the presence of marked adrenal involution, either spontaneous or induced by cortisone or hydrocortisone, a characteristic pattern of response may be of diagnostic aid. Initially, both the eosinophil and urinary steroid changes are subnormal, being followed by a progressive increase in the intensity of response. In some cases as long as five days of ACTH administration may be required to produce a normal level of adrenal response.

### *Bilateral Adrenal Hyperplasia*

The demonstration by Wilkins et al.[603] of the therapeutic effectiveness of continued cortisone administration to patients with bilateral adrenal hyperplasia has suggested the possibility of differentiating adrenal tumor and adrenal hyperplasia in patients with virilization. It was recently demonstrated that the prolonged administration of cortisone to patients with adrenocortical tumors, in contrast to those with bilateral hyperplasia, fails to produce a persistent depression of 17-ketosteroid excretion[601, 605] (Fig. 29). Dosage schedules are discussed below under treatment of bilateral adrenal hyperplasia.

### *Diabetes Mellitus*

The appearance of sustained hyperglycemia and glycosuria during treatment with ACTH, cortisone or hydrocortisone is considered to reflect a limited reserve capacity of the pancreatic islets to augment the level of insulin secretion. Therefore, patients who exhibit a diabetic response to ACTH or steroid therapy may justifiably be considered as cases of latent diabetes mellitus. It is suggested that the response to ACTH, cortisone or hydrocortisone should be investigated more thoroughly as a diagnostic aid in the detection of latent diabetes mellitus. It should be recognized, of course, that glycosuria alone may reflect only the action of these hormones on renal function.

### Adrenocortical Inhibition

The capacity of cortisone to depress the secretory activity of the adrenal cortex has prompted its use in the treatment of the adrenogenital syndrome due to bilateral adrenal hyperplasia. The careful studies of Wilkins et al.[81, 205, 221] have established the effectiveness of this form of therapy. Although the suppression of adrenal secretion should be as complete as possible, it is desirable to use the smallest dose of cortisone commensurate with continued suppression of adrenal activity to avoid untoward side effects. With the urinary output of 17-ketosteroids as a guide, doses must be determined for each patient. Treatment is usually initiated with intramuscularly injected cortisone at a dosage level of 50 mg. per day for older children and 25 mg. per day for younger children and infants. Maximum suppression of urinary ketosteroids occurs within five to ten days, after which maintenance doses should be instituted. The final level of 17-ketosteroid excretion obtained represents the balance between endogenous secretion from the adrenal cortex and the metabolic conversion of administered cortisone to urinary 17-ketosteroids. In general, a somewhat greater quantity of 17-ketosteroid is derived from orally administered cortisone than from an equal dose injected intramuscularly. For older children maintenance doses of 25 mg. per day are usually sufficient whereas in infants and younger children smaller doses are ordinarily effective. The maintenance suppressive doses of orally administered cortisone are approximately two or three times as great as those given by the intramuscular route.

Although it is too early to assess the long-term effect of cortisone on bilateral adrenocortical hyperplasia, the clinical results thus far observed are encouraging. Hirsutism has decreased, menstrual cycles are usually re-established, and the breasts may undergo progressive development. Hypertension may significantly decrease, and pigmentation ordinarily recedes.

### Pharmacologic Use

ACTH, cortisone and hydrocortisone have provided clinicians with a triad of therapeutic agents possessing a scope of physiologic and pharmacologic activities equaled by few drugs. It is apparent, therefore, that the physician employing these agents must possess a sound understanding of their multiple metabolic activities if the greatest benefit is to be derived and if undesirable side effects are to be minimized.

It was inevitable that the initial reaction to the widespread use of these agents in the treatment of crippling diseases previously refractory to available pharmacologic agents should be associated with considerable enthusiasm. Although time and experience have exerted a tempering effect on the over-all evaluation of their therapeutic efficacy, it is clear today that they have achieved a definite area of clinical usefulness. In certain specific situations, their use may be life saving. In others they provide a nonspecific means of controlling, at least temporarily, many metabolic, inflammatory and allergic disorders. Although these agents do not provide a *biologic cure* for a single known entity, their careful but imaginative use has created numerous and effective therapeutic approaches where none had previously existed. It must be emphasized, however, that the hormones serve in no way as substitution for standard measures of supportive treatment.

In contrast to the relatively well standardized program of substitution therapy employed in patients with adrenal and pituitary insufficiency, it is difficult to establish arbitrarily therapeutic programs for the wide range of disorders in which the hormones are used nonspecifically. Optimum dosage is not fixed; the metabolic and clinical responses of the patient, although generally predictable, are highly variable. It is therefore mandatory that the course of therapy undertaken with these agents be truly individualized. Furthermore, it is essential that the therapeutic effect obtained be evaluated in terms of the over-all metabolic changes produced to establish the dosage level that will provide maximal therapeutic benefits with minimal undesirable "side effects."

Patients suitable for hormone therapy may be classified as follows: those in whom this therapy may be life saving or may lead to a significant prolongation of life (for example, intensive hormone therapy is capable of salvaging, at least temporarily, the majority of patients with severe pemphigus); those in whom hormone treatment results in the restoration or preservation of certain essential functions (for example, the use of these agents in certain destructive inflammatory ocular diseases may prevent serious or total loss of vision); those with certain acute, self-limited inflammatory or allergic disorders, who may be relieved of discomfort and even disability by the administration of suppressive doses of ACTH, or steroids, during the natural course of these disorders (pruritus, erythema and exudation may be relieved in certain patients with contact dermatitis); and those with chronic disease, in whom steroid therapy may delay or modify the development of either destructive or fibrotic sequelae (the main example is rheumatoid arthritis). It should be re-emphasized that the decision to employ chronic hormone therapy demands a comparative evaluation of the potential gains and risks involved. Thus, a maintained conversion of patients with rheumatoid arthritis from Class III* (functional capacity limited to little or none of usual duties) to Class II* (functional capacity adequate for normal activities despite handicaps of discomfort or limited motion of one or more joints) may well warrant the induction of a mild state of hyperadrenalism; on the other hand, eliminating the chronic and relatively stationary lesions of discoid psoriasis rarely justifies the protracted use of hormone therapy. Similarly, hormone treatment is frequently indicated for the control of acute and severe exacerbations of a chronic disorder in which there is a reasonable possibility of spontaneous remission or in which standard methods of treatment may suffice to control the disease except during acute episodes. The use of ACTH and steroid therapy for the acute hemolytic crisis of acquired hemolytic anemia exemplifies this type of therapy.

The precautions to be taken before or during long-term ACTH and cortisone treatment were described in the previous section on Cortisone. It should be emphasized that laboratory data are in no way a satisfactory substitute for frequent careful clinical observations.

Dosage schedules cannot be arbitrarily established, but must be determined on the basis of the clinical response obtained. In general an effective initial response to ACTH is produced by the intramuscular administration of 50 to 100 *U.S.P.* units of a lyophilized preparation in divided doses at intervals of six to eight hours; the intramuscular or subcutaneous administration of 40–80 clinical units of ACTH in gelatin daily; or the daily intravenous infusion over an eight-hour period of 20 to 25 *U.S.P.* units of a lyophilized preparation. Once an adequate clinical response is produced, the total daily dose should be gradually reduced to maintenance levels. The ultimate objective in long-term therapy is to establish the minimal maintenance

*Classification of the American Rheumatism Association.

dose capable of sustaining a clinical remission. Should the clinical response to ACTH administration be inadequate, the production of an adrenocortical response should be verified.

For patients treated with cortisone or hydrocortisone an initial daily dose of 150 to 300 mg. is ordinarily effective. With intramuscular administration, a single daily injection is usually adequate. When the oral route is employed, hormone should be administered at intervals of six to eight hours. Once a satisfactory clinical response is established, dosage should be reduced gradually by decrements of 10 to 12.5 mg. until the lowest dosage level capable of maintaining a suitable therapeutic response is attained. The importance of exercising great care in tapering the dose of ACTH or cortisone when termination of hormone treatment is contemplated was discussed in the previous sections on Cortisone and ACTH.

During hormone therapy, certain readily observable alterations in the patient's clinical condition serve as practical guides for evaluating the intensity of the metabolic and therapeutic response. An improved sense of well-being and an increase in appetite may appear early in the course of therapy. Fever is ordinarily reduced, often within hours of the initiation of treatment. Conversely, a rise in temperature during a program of dosage reduction directly suggests either an inadequate dosage level or a superimposed complication. The disappearance of pain and the inhibition of the classic signs of inflammation reflect a satisfactory therapeutic effect. A suppression of the patient's inflammatory responses, however, imposes upon the physician the obligation of continual alertness to the possible occurrence of a masked infection.

In most cases the type and severity of a pathologic process do not determine the hormonal agent (ACTH, cortisone or hydrocortisone) to be employed. In some cases the threat of complications may justify the choice of one agent. For example, in the presence of marked hypertension or cardiac decompensation, the use of cortisone or hydrocortisone may be considered preferable because of a somewhat less intense initial sodium and water retention than that encountered during ACTH therapy. On the other hand, certain patients with severe disseminated disease such as pemphigus have sometimes not responded well to doses of cortisone as large as 500 mg. per day, but have demonstrated a prompt improvement during intensive treatment with ACTH. For the local treatment of joint, eye or skin disease, hydrocortisone has been found to be considerably more effective than cortisone, as pointed out in the section on Hydrocortisone.

*Mesenchymal Diseases*

A major field for the therapeutic trial and evaluation of ACTH and cortisone has been in a group of disorders of unknown pathogenesis that affect primarily the mesenchymal tissues. These diseases include rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, polyarteritis nodosa, dermatomyositis and scleroderma. Although nearly four years of clinical experience have demonstrated that the effects of these agents may be dramatic and even life saving, neither a precise delineation of the mechanisms of the action nor a final evaluation of the effects of hormone therapy on the ultimate clinical course of these diseases is possible at present.

*Rheumatoid arthritis.* Since the original description by Hench et al.[109] of the use of cortisone and ACTH in the treatment of rheumatoid arthritis, numerous confirmatory reports have appeared. It is common knowledge that in the vast majority of cases the administration of adequate suppressive doses of these agents results in a marked improvement in the patient's general condition. Articular pain and stiffness decrease, joint swelling diminishes, and the range of motion and muscle strength increases. Appetite is increased, weight loss is arrested or reversed, fever and pulse are reduced toward normal levels, and the anemia is diminished. Initial doses of cortisone by mouth are usually in the range of 150 to 300 mg. per day. Initial doses of ACTH are 20 to 25 *U.S.P.* units intravenously (eight-hour infusions), 75 to 150 *U.S.P.* units per day of the lyophilized preparations, or 40 to 80 clinical units in gelatin. When the active pathologic process appears to have been controlled, dosage is gradually reduced.

The intra-articular injection of hydrocortisone in doses of 25 to 50 mg. has been shown to be of use in patients with joint disease of limited distribution and in some patients in whom systemic steroid therapy produces definite but incomplete improvement. The indications and methods for the local use of this agent have been well described by Hollander.[221]

Symptomatic relief ordinarily persists throughout hormone administration. After withdrawal a relapse generally occurs, usually within a period of days and nearly always within four to eight weeks. Occasionally, prolonged remissions follow the initial period of repressive treatment. In the great majority of patients, however, long-term therapy is required to maintain symptomatic control. It is primarily in relation to the indications for, and the efficacy of, maintenance hormone therapy in chronic diseases, of which rheumatoid arthritis is the prime example, that differences in clinical opinion currently exist. A compromise between complete subjective and objective control on the one hand and the occurrence of undesirable side effects of hormone therapy on the other is usually necessary. In general, dosage requirements for maintenance therapy are determined by the intensity of the pathologic process and the level of physical and emotional activity of the patient. Maintenance doses are therefore not fixed but vary with fluctuations in the activity of

the inflammatory process and the over-all mental and physical state of the patient. Unfortunately, in some patients the dosage level required to maintain adequate symptomatic control increases progressively as therapy is continued.

In evaluating the results of long-term maintenance therapy, Hench[606] has distinguished three groups:

> The patients in group 1 have been controlled rather easily by apparently safe, relatively low maintenance doses. Adjustments in the dose were occasionally necessitated by spontaneous flares, trauma or intercurrent infections. At least 50 per cent of patients have fallen into this group. Patients in group 2 (about 35 per cent) have required closer attention and more frequent changes in the doses. In such patients increased doses, temporarily required, may induce side effects for which supplemental measures may be needed transiently. These patients have been more difficult to handle than those in group 1, but the results are often quite satisfactory. In group 3 (about 15 per cent) the continuous adequate control of the disease with tolerable doses has been difficult, if not impossible, using present schemes of hormonal treatment, because of the severity of the disease or other poorly understood factors.

In a recent report by Polley et al.[607] on the use of cortisone in the maintenance treatment of rheumatoid arthritis, side effects were encountered in 63 per cent of patients receiving 75 mg. or more per day, but in only 21 per cent of patients receiving 62.5 mg. or less daily. Boland[608] has stated that approximately two thirds of patients with this disease can be safely maintained on doses of 37.5 to 100 mg. of cortisone acetate per day. Holbrook[608] reported that maintenance therapy over a period of more than two years was possible in approximately 25 per cent of patients treated with ACTH. However, better results might well be obtained with the more highly purified preparations of ACTH currently available.

Bauer[609] has divided patients into three groups: those with inactive disease and irreversible joint deformities, who gain little from hormone treatment; those with varying degrees of inflammatory activity and symptoms markedly influenced by environmental or emotional factors, who are often difficult to control and may even prefer that therapy be discontinued; and those with active disease in whom correlation between the intensity of the pathologic process and the degree of disability is reasonably close and in whom hormone therapy is the most effective. Symptomatic improvement and increased functional capacity are the most impressive effects of hormone therapy in rheumatoid arthritis and are usually out of proportion to the objective changes observed. Although a marked increase in the patient's functional capacity may be achieved with continued treatment, histologic and radiologic evidence of progression of the disease persists. Although Bauer has found continued maintenance therapy to be feasible in approximately 60 per cent of patients treated with cortisone, only 37 per cent have progressed from advanced or complete disability to a state commensurate with active work, but with some handicap and discomfort; only 9 per cent have achieved full functional capacity.

Children with Still's disease usually respond well to therapy. In view of the poor ultimate prognosis in this disorder,[610] treatment appears to be indicated when other measures have failed and the hormones can be effectively employed without too intense side effects.

Of the patients with active rheumatoid arthritis, many with mild disease who improve during hormone therapy might well be successfully managed without steroid treatment. Patients with severe active disease, on the other hand, often require large doses of hormones, and the results are frequently disappointing, with little or no increase in the range of joint motion or muscle strength. Although ACTH or cortisone therapy has often been recommended in these patients to facilitate the institution of adequate physical therapy, hormone withdrawal is usually followed by relapse so that continued rehabilitation depends upon the continuation of hormone administration. Ragan[611] has emphasized the fact that the most important use of steroid therapy in patients with rheumatoid arthritis is in the treatment of the early case with a poor prognosis as indicated by an early and rapid progression of the disease, a failure to respond to salicylates and bed rest, a positive agglutination against hemolytic streptococci and a positive sensitized sheep-cell agglutination early in the disease. In such patients early and sustained treatment appears to have at least slowed the march of the disease even though the disease process has not been completely repressed:

> The crying need in the present treatment of rheumatoid arthritis is for an understanding of the pathogenesis of the disease, particularly its etiological factors, and for some definitive indices of a poor prognosis early in the disease. With the latter available, the tools are at hand to prevent invalidism, at least for some years. These tools all have dangers or disadvantages but with assurance that a reasonably certain invalidism might be avoided, the dangers and disadvantages could be faced much more squarely than is possible in our present state of indecision.[611]

*Rheumatic fever.* The treatment of acute rheumatic fever with ACTH and cortisone has recently been critically evaluated by Massell.[612] That these agents might be useful in the treatment of rheumatic fever was first suggested by Hench and his coworkers.[103] Although it is generally agreed that these hormones may suppress the manifestations of acute rheumatic fever, there is no complete agreement about the degree of their suppressive effect or whether the actual duration of the acute attack may be shortened. Even if the attack is not reduced in duration, ACTH and cortisone may still prove to be useful in the treatment of acute rheumatic fever. By suppression of the inflammation in the heart it should be possible to prevent congestive heart failure and to lessen the amount of fibrosis and valvular deformity that are the consequence of the healing process. For the most effective thera-

peutic application of ACTH and cortisone the diagnosis of acute rheumatic fever must be made promptly, treatment instituted early, the hormones administered in a dose sufficient to cause a maximum degree of suppression of the inflammatory process, and treatment with a suppressive dose of the agent continued until the attack has subsided.

Of all the symptoms and signs of acute rheumatic fever that may be influenced by hormone treatment, fever and polyarthritis come most rapidly under control, usually subsiding completely within one or two days of the initiation of therapy. Subcutaneous nodules become significantly smaller within seven to fourteen days of the beginning of hormone treatment and finally disappear by the end of four to eight weeks. The erythrocyte sedimentation rate begins to fall within three to seven days and has usually returned to a normal level within one to three weeks. Pericarditis diminishes within three or four days and disappears within a period of a few days to two weeks. Gallop rhythm and a prolongation of the PR interval usually respond to cortisone and ACTH treatment. Congestive heart failure may be aggravated during the first few days. Within a week or ten days, however, one ordinarily finds that congestive failure can be more readily controlled by the usual measures than it could by the same measures before the administration of cortisone and ACTH.

Although cortisone and ACTH may suppress the majority of the manifestations of acute rheumatic fever, it is still uncertain whether these agents possess significant advantages over salicylates in the treatment of this disease. At present, a cooperative study of this problem is being conducted in the United States, Great Britain and Canada by the Council on Rheumatic Fever of the American Heart Association in conjunction with the British Medical Research Council. In a preliminary report[613] based on analysis of approximately 300 cases, it was stated that no firm conclusions could be drawn concerning which of the three drugs (salicylate, ACTH and cortisone) is most effective in the control of acute rheumatic fever. It was believed that the patients had not been under observation sufficiently long to provide information on the prevention of rheumatic heart disease. Massell,[613] however, doubts whether even toxic doses of salicylates can suppress the acute inflammatory reaction as well as large doses of ACTH or cortisone. Massell uses 200 mg. of cortisone daily by oral administration for three or four weeks, gradually tapering the dose over the course of the following six to ten weeks. ACTH gel is employed in a dose of 120 clinical units per day by intramuscular injection for three or four weeks, after which the dose is gradually diminished over the following six to ten weeks. The results obtained with these therapeutic programs in acute rheumatic carditis appear to surpass those achieved with the more conservative courses of hormone treatment used in the co-operative study described above.

It has become apparent from a number of studies[614-617] that patients who have mild active rheumatic carditis of many months' duration usually benefit little from ACTH and cortisone treatment. Furthermore, the dosages required to achieve a satisfactory repression of the chronic inflammatory reaction are often excessive, resulting in a high incidence of untoward side effects. The response of chorea to hormone therapy has been variable, and further study is required. Patients who have rheumatic heart disease that is inactive need not be treated with ACTH and cortisone. Adrenocortical hormones are not indicated in cases of advanced heart disease and congestive heart failure in which failure has a mechanical basis. The patients most suitable for hormone therapy are those with acute rheumatic fever and carditis of recent onset. In this situation, it is still questionable whether ACTH and cortisone are of greater value than salicylates. Finally, it is still too early to evaluate the extent to which the hormones may inhibit the development of permanent cardiac damage after the subsidence of active rheumatic carditis.

*Disseminated lupus erythematosus.* ACTH, cortisone and hydrocortisone are the most effective agents available for the treatment of generalized lupus erythematosus,[618-620] and their use may result in a significant prolongation of life. The administration of suppressive doses ordinarily causes a prompt remission in fever, serositis, arthritis, skin rash and mucosal lesions. Anemia is reduced, especially in patients with minimal renal involvement, but the abnormal L. E. cells of Hargreaves usually persist. Evidences of acquired hemolytic anemia and purpura that may occur are usually well controlled. In critically ill patients heroic therapy (40 to 60 *U.S.P.* units of ACTH or 300 to 500 mg. of cortisone or hydrocortisone by continuous intravenous infusion) may be required to induce remission. Relapse frequently follows hormone withdrawal and must be controlled by either maintenance treatment or intermittent courses of suppressive treatment. Unfortunately, renal damage is not ameliorated by hormone therapy except in certain patients with early nephritis, and the ultimate prognosis must therefore be guarded.

*Polyarteritis nodosa.* The administration of ACTH and cortisone has been shown to be effective in repressing, at least temporarily, many of the manifestations of polyarteritis nodosa.[621, 622] Initial doses must be large in patients who are critically ill. Maintenance therapy is usually necessary for continued symptomatic control, but prolonged remissions have sometimes been observed after

intensive treatment with suppressive doses. Some evidences of residual vascular damage persist in most patients, however. As in disseminated lupus erythematosus, renal lesions are usually quite refractory to treatment. Two special hazards of hormone therapy in these patients deserve emphasis: although widespread vascular healing may occur, fibrous obliteration of these vessels may result in extensive and even fatal visceral infarctions; in some cases hormone therapy has been associated with the development of malignant hypertension.[622] It is evident, therefore, that treatment of this disease with ACTH and steroids is highly indicated but is more effective and less hazardous in early cases in which widespread vascular damage has not yet occurred.

*Allergic Diseases*

The therapeutic effects of cortisone and ACTH in allergic disorders have been reviewed by Evans and Rackemann.[677] Suppressive doses have resulted in either marked or complete control of symptoms in approximately 85 per cent of patients with acute bronchial asthma refractory to other methods of treatment. Treatment may be especially valuable in patients with status asthmaticus who are not responding well to the usual therapeutic agents. In these cases the continuous intravenous administration of ACTH (20 to 25 *U.S.P.* units) and cortisone or hydrocortisone (100 to 200 mg.) has proved particularly effective. Continued symptomatic control ordinarily requires long-term therapy, and in some patients persistent relief may be obtained with comparatively small doses such as 50 mg. of cortisone acetate orally per day. At present, hormone therapy is indicated in patients with severe asthma only when the usual methods of treatment are inadequate.

In most cases the symptoms of hay fever and vasomotor rhinitis can be temporarily controlled by the administration of ACTH and cortisone, but the dosages necessary are ordinarily as large as those required for the treatment of asthma. Nasal polyps may decrease in size and even disappear. Local treatment with hydrocortisone may be effective in these disorders and has the advantage of obviating the occurrence of untoward side effects. Hormone therapy, however, is rarely indicated.

The use of ACTH and cortisone in the treatment of acute drug reactions has been described by Carey et al.[624] and others. Response to hormone therapy is usually prompt, and comparatively small doses of the hormones often suffice. The duration of treatment depends on the type and severity of the reaction. In a significant number of cases relapse follows hormone withdrawal so that retreatment is necessary. These agents have proved effective in the treatment of reactions resulting from penicillin, gold, iodine, atropine and other drugs.

The use of cortisone and ACTH in the treatment of contact dermatitis, atopic dermatitis and the mesenchymal diseases is described elsewhere.

*Trauma and Infection*

In view of the known importance of adrenocortical hormones in the mechanisms of response to acute severe stress,[278] an extensive literature has accumulated concerning the effects of these agents in patients with traumatic shock, extensive burns and other forms of major stress.[625,626] The results of these studies have often been conflicting and inconclusive, but in most cases no beneficial effect of hormone therapy in shock has been evident in patients with adequate adrenocortical function. With solutions of crystalline steroids now available for clinical use, however, the entire problem undoubtedly deserves to be re-evaluated. The procedure of choice would be the continuous intravenous infusion, after an initial priming dose, of large doses of hydrocortisone or cortisone. Despite early encouraging reports, recent experience has not confirmed the beneficial effect of adrenal steroids on either capillary permeability or the viability of skin grafts in patients with severe burns.[627, 628]

The administration of ACTH or steroids to patients with severe infections such as typhoid fever,[629] pneumonia[344] and peritonitis[630] has been described. Although fever and other "toxic" manifestations may be ameliorated, the infectious agent is not directly affected. *It should be emphasized that hormone therapy should, in general, not be undertaken in the presence of an infection unless the organisms can be effectively controlled.* For this purpose bacteriocidal rather than bacteriostatic levels of antibiotic activity are to be preferred since the humoral and cellular mechanisms of defense may be impaired by intensive steroid therapy.

*Metabolic Disease*

McQuarrie[631] demonstrated that comparatively small doses of ACTH are capable of maintaining normal blood sugar levels in infants with spontaneous hypoglycemia and in some patients with glycogen-storage disease or pancreatic beta-cell adenomas. Long-term hormonal therapy of patients with hypoglycemia should be reserved for those in whom no definitive etiologic factor (for example, islet-cell tumors) can be demonstrated.

The early studies of Hellman[632] and of Wolfson and his associates[633] showed that the administration of ACTH could terminate an acute attack of gouty arthritis; unfortunately, withdrawal of hormone was frequently followed by an acute relapse. These observations have been repeatedly confirmed. Although an attack of acute gouty arthritis can usually be effectively and rapidly relieved by the intramuscular injection of 80 to 120 clinical units of ACTH in gelatin or the continuous intravenous in-

fusion of 20 to 25 *U.S.P.* units of ACTH over a period of eight to twenty-four hours, it is essential that colchicine administration be instituted simultaneously to prevent a recurrence of the attack after hormone withdrawal.[624] The relief produced appears to depend chiefly on the antiphlogistic action of the hormones since it has been frequently demonstrated that the acute attack may subside before a significant degree of uricosuresis has been observed. Since symptomatic relief may be rapidly achieved, the availability of ACTH and cortisone for the treatment of acute gouty arthritis constitutes a significant therapeutic advance,[625] particularly in patients who respond poorly to colchicine therapy. It appears preferable at present to depend primarily upon nonhormonal uricosuric agents (such as salicylates and benemid) for the treatment of interval gout.

The findings of Szilagyi et al.[626] concerning the beneficial effect of adrenocortical hormones in patients with acute thyroid crisis suggest that the intravenous infusion of cortisone or hydrocortisone may prove to be of value in the treatment of this disorder.

*Neoplastic Disease*

The role of ACTH and cortisone in the treatment of neoplastic disease has been reviewed by Nathanson and Kelley.[627] The hormones have been found to be ineffective in a wide variety of carcinomas, including carcinoma of the breast, esophagus, gall bladder, stomach, colon, pancreas, trachea, lung, cervix, testes, kidney and adrenal gland, and neoplastic disease of connective-tissue origin, including fibrosarcoma, neurofibrosarcoma, rhabdomyosarcoma, malignant melanoma, synovioma, neuroblastoma, osteogenic sarcoma and Ewing's tumor.

In approximately 20 per cent of a small series of cases of multiple myeloma treated with ACTH and cortisone there has been relief of pain, improvement of strength, reduction in serum globulin, decline in excretion of Bence-Jones protein, improvement in anemia and a decrease in marrow plasmablasts. No change in the osseous lesions has been observed, and relapse has usually occurred shortly after termination of therapy.

Nathanson and Kelley[627] have critically appraised the role of ACTH and cortisone in the treatment of leukemia and lymphoma. They conclude from a review of a large number of reports that complete or partial remission, lasting from a few days to several weeks, may follow the administration of ACTH and cortisone in a moderate number of cases of acute and subacute leukemia. The most favorable results have been obtained in children with a lymphatic type of acute leukemia. Occasional responses have been reported in acute myelogenous, eosinophilic and monocytic leukemia. In a number of cases the hormones appear to have accelerated the course of myelogenous leukemia. A few patients with chronic lymphatic leukemia have been benefited temporarily by ACTH or cortisone treatment, but the improvement has been less well sustained than that obtained with x-ray therapy.[628] Short-lived partial remissions of Hodgkin's disease, lymphosarcoma and leukemia cutis have been observed. In the vast majority of cases of leukemia or lymphoma in which the first course of hormone therapy has been of temporary benefit, response to further courses has progressively diminished or failed altogether. Some cases of acute leukemia have responded more effectively to combined therapy with folic acid antagonists and cortisone or ACTH than to either agent alone.[629] Similar results have occasionally been obtained in patients with lymphoma when ACTH or cortisone has been given with nitrogen mustard. Moreover, the hormones may minimize the undesirable effects of nitrogen mustard therapy.[630]

The clinical course of some patients in the terminal phase of malignant neoplastic disease can be materially eased by the judicious use of ACTH or steroid therapy. Pain may be lessened, appetite improved, and a sense of well-being at least partially restored. This type of hormone usage constitutes treatment of the patient rather than of his basic disease and represents an extreme example of the nonspecific use of these agents.

*Diseases of Skin*

In discussing the use of these agents in the treatment of cutaneous disorders, Lever[376] has clearly defined the indications for hormone therapy in skin diseases under four headings:

> The first comprises serious, frequently fatal dermatoses in which ACTH or steroid therapy affords the most effective treatment available and in which, therefore, their use is highly indicated. This group includes pemphigus, chronic idiopathic generalized exfoliative dermatitis, dermatomyositis, and disseminated lupus erythematosus. All forms of pemphigus respond to hormone therapy. Dosage in severe cases must be high to induce remission (20 to 40 *U.S.P.* units of ACTH by continuous intravenous infusion for periods of eight to twenty-four hours, 100 to 200 clinical units of ACTH gel intramuscularly or 300 to 500 mg. cortisone acetate per day). Once remission is produced continued treatment with relatively high maintenance doses is essential.
>
> The response to ACTH or steroid therapy in patients with generalized exfoliative dermatitis is ordinarily excellent, and considerably smaller doses than those required in pemphigus are often adequate. Maintenance treatment is usually required to prevent relapse.

In dermatomyositis intensive treatment with ACTH or cortisone may sometimes produce a rapid improvement of symptoms. In some patients prolonged remissions of one year or more have resulted. Once the disease is controlled, the administration of testosterone may be of value in maintaining the remission and in restoring muscular tissue. It is important to initiate therapy early since advanced muscular destruction is irreversible.

Disseminated lupus erythematosus is discussed above in the section on mesenchymal diseases.

The second group, acute, self-limited inflammatory disorders in which ACTH and steroids are effective and treatment is indicated if the symptoms are severe,[643] includes drug eruptions, erythema multiforme, anaphylactoid purpura and contact dermatitis. Erythema multiforme ordinarily responds well to treatment with these agents. Therapy may be indicated in severe cases, particularly in those with extensive mucosal involvement. The response to hormone therapy in anaphylactoid purpura is usually adequate with the exception of the nephritis, which may be a prominent manifestation in some patients. In contact dermatitis, it is, of course, imperative to remove the causative agent. In severe cases, however, it may be useful to administer a short course of hormone therapy to shorten the period of disability. Drug eruptions are discussed above under allergic disorders.

The third group, chronic dermatoses in which ACTH and cortisone are indicated only in exceptional circumstances,[642] consists of psoriasis, chronic eczema (including atopic dermatitis), dermatitis herpetiformis and chronic discoid lupus erythematosus. These diseases ordinarily respond promptly to treatment with ACTH or cortisone. After cessation of therapy, relapse usually occurs just as promptly, and often the disease is more severe in relapse than before treatment was instituted. To control these disorders, therefore, long-continued therapy is required. Except in severely disabled patients, such as those with generalized exfoliative psoriasis, treatment with steroids or ACTH is not justified, and the standard procedures of dermatologic therapy should be employed.

The final group, chronic, serious dermatoses in which ACTH or cortisone is of little value, includes scleroderma and mycosis fungoides. Hormone therapy may benefit, although temporarily, the early inflammatory lesions of scleroderma. Response of the fibrotic lesions in advanced cases is slight.

*Musculoskeletal Disease*

One of the earliest instances of the therapeutic use of adrenal hormones in human disease was the trial by Soffer et al.,[643] in 1948, of ACTH in patients with myasthenia gravis. In the majority of patients the disease is aggravated during hormone administration; in rare cases death has occurred. After hormone withdrawal, however, muscular function may improve, resulting in a decreased requirement for neostigmine. In view of the potential dangers involved, treatment of myasthenia gravis with these agents is not recommended except in highly specialized hands.

A decrease in myotonic response has been observed during intensive cortisone and ACTH therapy in patients with dystrophia myotonica, but without significant improvement in the muscular or visceral dystrophies. Improvement in muscular strength and endurance has been described in the muscular dystrophy of menopausal women.[224] Treatment of other forms of myopathies has not proved beneficial.

Cortisone, hydrocortisone and ACTH may be extremely useful in the treatment of bursitis and calcific tendonitis.[644] The intravenous infusion of ACTH over an eight-hour period for one or two days often provides almost complete relief from pain, accompanied by a marked increase in mobility. The local injection of hydrocortisone into inflamed bursas in a dose of 25 to 50 mg. ordinarily results in prompt clinical improvement. The therapeutic results of manipulation of the "frozen" painful shoulder are considerably enhanced by the concomitant administration of ACTH or steroid hormones. For example, the continuous intravenous infusion of ACTH during a period of eighteen to twenty-four hours before manipulation and for a similar period after the procedure may markedly reduce pain, thereby facilitating both passive and active mobilization of the joint.

*Gastrointestinal Disease*

The use of ACTH and cortisone in the management of gastrointestinal disorders has been reviewed by Halsted.[645] The development of gastric or duodenal ulcers or the aggravation of persisting peptic ulcers in patients under treatment with cortisone or ACTH has been the subject of numerous reports. It is clear that therapy with ACTH or cortisone is absolutely contraindicated in the presence of an active peptic ulcer.

In patients with nontropical sprue who have not responded to dietary management and folic acid or vitamin $B_{12}$, oral cortisone therapy may produce dramatic improvement.[210, 646, 647] There is an increase in appetite, weight and sense of well being, a disappearance of diarrhea, a fall in fecal fat and nitrogen content and a return of serum protein and prothrombin to normal levels. On occasion it has been possible for the patient to resume a normal diet. In the majority of cases, continued therapy with cortisone is necessary to maintain a partial or complete remission of the disease. In most cases,

however, the dose of cortisone required for this purpose is so small (50 to 75 mg. per day) that undesirable side effects are rare.

ACTH and cortisone may be of value in the treatment of patients with ulcerative colitis who have failed to respond to supportive therapy.[648, 649] The most satisfactory remissions occur in the early stages of the disease in patients with severe symptoms of short duration. In these cases there is often an impressive increase in sense of well-being, appetite and weight, a disappearance of fever, a marked diminution of abdominal pain and diarrhea and a fall in fecal blood and lysozyme content. ACTH and cortisone have little effect on patients who have had ulcerative colitis for many years, particularly if complications such as stricture, polyps and fistulas have occurred. In both the acute and chronic phases of the disease hormone therapy may be of considerable help in the preparation of patients for ileostomy. In approximately half the patients, relapse of the disease occurs shortly after cessation of hormone therapy. In the remainder, there is a variable period of remission, which may last in occasional cases as long as a year or more. Unfortunately, the doses of cortisone required to maintain a remission are usually so large (not less than 75 mg. per day) that undesirable side effects are frequent.

Regional ileitis responds in similar fashion to ACTH and cortisone treatment, and the therapeutic considerations described for ulcerative colitis may be applied to this disease.

*Hepatic Disease*

The benefits to be obtained from the use of ACTH and cortisone in the treatment of acute viral hepatitis[650] and chronic hepatic disease[207, 651] are largely nonspecific. Appetite may be markedly stimulated, pruritus may be reduced, and serum bilirubin and bile acid levels are frequently lowered, particularly in patients with cholangiolitic biliary cirrhosis.[652] It is doubtful, however, whether the course of liver disease is significantly altered. Moreover, there appears to be an increased incidence of untoward side effects, such as portal thrombosis, edema and ascites, in these patients. Recently Ducci and Katz[653] reported that the administration of large doses of cortisone and ACTH to patients with hepatic coma due to fulminating hepatitis resulted in striking clinical improvement and subsequent recovery. A similar effect has been obtained with intravenous infusions of cortisone and hydrocortisone in 2 patients in the Medical Clinic of the Peter Bent Brigham Hospital.

*Diseases of the Nervous System*

The effects of ACTH and cortisone in various disorders of the nervous system have been reviewed by Merritt.[654] No beneficial effects have been obtained in patients with amyotrophic lateral sclerosis, anterior poliomyelitis, cerebromaculodegeneration, Wilson's disease and Parkinson's disease. No improvement has occurred in the majority of patients with multiple peripheral neuritis and idiopathic epilepsy.

Approximately a third of the patients with multiple sclerosis treated with ACTH or cortisone have been reported to show changes suggestive of improvement in the ataxic, spastic-paretic and acute visual manifestations. In most cases improvement has been temporary. The effects of prolonged therapy on the ultimate course of the disease remain to be determined. The difficulties of evaluating pharmacologic agents with potent nonspecific effects in a chronic disease characterized by wide spontaneous fluctuations in clinical course are obvious.

The most important application of hormone therapy in nervous-system disorders has undoubtedly been the successful treatment of acute optic and retrobulbar neuritis, occurring either as a manifestation of multiple sclerosis or as an independent phenomenon.[655] A lessening of pain, a decrease in the size of scotomas and a significant increase in visual acuity have been achieved in a high percentage of cases. Although spontaneous remissions certainly occur in this disorder, the frequency with which good therapeutic results have been achieved during ACTH or cortisone therapy suggests that these agents are indeed responsible. Quinn and Wolfson[656] have emphasized the fact that prolonged treatment at high dosage levels may be effective even in chronic, apparently irreversible, cases of optic neuritis. Once a significant degree of improvement is induced, dosage may be gradually reduced to maintenance levels.

*Hematopoietic Disease*

The use of ACTH and cortisone in the treatment of hematopoietic disease has been discussed by Wintrobe et al.[657] and by Stickney and Mills.[658] Patients with acquired hemolytic anemia, either idiopathic or secondary to lymphoma and leukemia, have improved as a result of intensive treatment with ACTH and cortisone.[655, 659] Although improvement has often been associated with a decline in the Coombs titer and a disappearance of abnormal agglutinins from the serum, satisfactory responses have sometimes occurred in the absence of an alteration in antibody titer. It is possible that ACTH and cortisone influence splenic sequestration and phagocytosis, as well as the humoral mechanisms involved.[660] Relapse usually occurs after termination of hormone therapy. Nevertheless, ACTH and cortisone may be of considerable value in the management of patients with acquired hemolytic anemia, for the control of a hemolytic crisis, for the induction of a remission in order that splenectomy may be more safely performed and for the treatment of

patients who have not been benefited by splenectomy.

ACTH and cortisone may be effective in the crises of sickle-cell anemia and, if therapy is maintained, may halt the progression of Cooley's anemia.[661] The hormones may be of value in controlling the hemolytic process associated with agnogenic myeloid metaplasia.[662] ACTH and cortisone have not been shown to prevent erythroblastosis fetalis. Whereas most patients with hypoplastic or aplastic anemia have failed to respond to hormone treatment, in a few cases continued therapy has resulted in a remarkable stimulation of bone-marrow activity.[663] In agranulocytosis secondary to drug intoxication the hormones may speed the return of neutrophils to the peripheral blood.[664, 665]

The use of ACTH and cortisone in idiopathic thrombocytopenic purpura has been critically appraised by Stefanini et al.[666] Although a rise in the number of circulating platelets may be induced in both the acute and chronic varieties of the disease, bleeding may be controlled in the absence of a platelet response, the hormonal effect probably being due in large part to a beneficial influence on capillary resistance as described by Robson and Duthie.[256] In view of the common occurrence of spontaneous remissions in acute idiopathic thrombocytopenic purpura, it is difficult to assess the value of ACTH and cortisone. As in acquired hemolytic anemia, the hormones may prove useful in the preparation of patients for splenectomy and in the control of the disease in patients who have not benefited from splenectomy.

The place of ACTH and cortisone in the treatment of the leukemias, lymphoma and multiple myeloma is discussed above under neoplastic disease.

*Pulmonary Disease*

In patients with chronic pulmonary granulomatosis due to sarcoidosis or exposure to beryllium a severe and progressive impairment of pulmonary respiratory function frequently develops. The effects of hormone treatment are in most cases sufficient to permit a significant restoration of pulmonary reserve.[667, 668] Discontinuation of therapy is ordinarily followed by clinical relapse, and, unfortunately, in some cases the response to repeated courses of treatment progressively declines.

Some patients with idiopathic pulmonary fibrosis derive marked symptomatic relief from prolonged treatment with cortisone, hydrocortisone or ACTH. In other cases no significant change in pulmonary function occurs. Since the ultimate fate of these patients is likely to be a severe respiratory insufficiency, it appears advisable to supplement antibiotic and other therapeutic measures with an adequate trial of ACTH or cortical steroid therapy. If an improvement in pulmonary function results, long-term therapy is usually mandatory.

Patients with Loeffler's syndrome have usually demonstrated a prompt resolution of lesions during hormone therapy, but maintenance treatment is generally necessary for continued symptomatic control.[669]

*Kidney Disease*

The most striking single fact concerning the influence of ACTH and cortisone on renal disorders is the almost complete absence of a beneficial effect in acute nephritis.[188] Indeed, the disease may actually be aggravated during hormone therapy. Similarly, chronic glomerulonephritis is not improved and the administration of large doses of either cortisone or ACTH may be associated with an elevation of blood pressure and, in rare cases, a rapid and marked increase in nitrogen retention.

In the nephrotic syndrome, however, ACTH, cortisone and hydrocortisone are probably the most effective agents available at present for the induction of a substantial diuresis.[189, 670, 671] The hormones are effective in approximately 50 to 75 per cent of patients treated. In cases in which diuresis fails to occur, an immediate intravenous course of salt-free human serum albumin will often produce a satisfactory response.[670] The persistent failure of diuresis to appear may signify progression of the disease to chronic glomerulonephritis. Prolonged remissions lasting many months have occurred after a successful course of ACTH or steroid treatment,[672] but in most cases edema gradually reaccumulates. Treatment with ACTH is ordinarily carried out over a period of ten to twelve days. Dosage for children under 50 pounds in weight varies from 60 to 80 *U.S.P.* units per day in four divided doses when the regular lyophilized preparations are administered by intermittent intramuscular injection. Children weighing over 50 pounds and adults may require a total daily dosage of 80 to 150 *U.S.P.* units. When ACTH gel is employed, a dosage of 40 clinical units ordinarily suffices for smaller children; for older children and adults a single daily dose of 60 to 80 units is usually adequate. It is essential that therapy be terminated abruptly. In some patients diuresis may occur before the completion of the course of ACTH therapy. When cortisone is employed, treatment is ordinarily carried out over a period of five to ten days. The hormone is administered orally, and dosage varies between 300 and 500 mg. per day. In our experience, no significant difference in the effectiveness of ACTH and cortisone has been noted.

*Diseases of the Eye*

The use of ACTH, cortisone and hydrocortisone in the treatment of a wide variety of ocular disorders has provided a new approach to the treatment of inflammatory diseases of the eye. The subject has been ably reviewed by Smith and Steffensen[421]

and Gordon and McLean.[673] Steffensen[419] has classified ocular diseases responding to ACTH or steroid therapy as follows:

*Favorable response*

Allergic conjunctivitis
Blepharoconjunctivitis
Vernal conjunctivitis
Episcleritis
Phlyctenular keratoconjunctivitis
Marginal ulcer
Keratitis
  Tuberculous
  Sclerosing
  Acne rosacea
  Profunda (non-specific)
  Superficial (non-specific)
  Syphilitic interstitial
Non-granulomatous uveitis, acute anterior
Non-granulomatous uveitis, acute posterior
Non-granulomatous uveitis, acute diffuse
Acute focal choroiditis
Acute optic neuritis
Acute retrobulbar neuritis
Central angiospastic retinitis
Sympathetic ophthalmia
Burns, chemical and thermal
Glaucoma, postoperative

*Variable response*

Herpes zoster ophthalmicus
Nongranulomatous uveitis, chronic anterior
Nongranulomatous uveitis, chronic posterior
Uveitis granulomatous, chronic anterior
Uveitis granulomatous, chronic posterior
Sarcoid uveitis
Erythema multiforme
Retinitis pigmentosa
Exudative retinitis

It is evident that the use of ACTH, cortisone and hydrocortisone is of greatest value in the treatment of nonspecific inflammatory lesions of the eye. The therapeutic action extends to all ocular coats, the optic nerve and the lids. Acute lesions of recent onset are most favorably influenced. As in pathologic processes elsewhere in the body, self-limited disorders, such as nongranulomatous iritis, provide an ideal indication for therapy, and the relapse rate is correspondingly low in disorders of this type.

Pain and photophobia are relieved, neovascularization is reduced, and the destructive consequences of severe inflammatory lesions are often prevented. The capacity of these agents to inhibit fibroplasia has done much to prevent symblepharon formation in chemical and thermal burns. Although results are in general less satisfactory in the treatment of chronic inflammatory lesions, a suitable maintenance program, aimed at the prevention of relapse, is often possible. For the most part, degenerative eye disease does not respond favorably to treatment with these agents.

The dosages of ACTH and nontopical cortisone or hydrocortisone are comparable to those required for the control of other inflammatory disorders. ACTH and systemically administered cortisone or hydrocortisone are recommended for the treatment of diseases that affect deep ocular structures and for the prompt control of severe acute lesions of the anterior segment. Topical administration of cortisone or hydrocortisone is mainly employed in inflammatory lesions of the anterior segment and may also be of use in preventing relapse of chronic anterior lesions treated initially by parenteral hormone administration. Eventual resistance to the therapeutic activity of topically administered cortisone, however, has been reported.[419] Preliminary experience indicates that the topical application of hydrocortisone may be somewhat more effective than cortisone.[421]

The successful treatment of inflammatory ocular disease with cortisone, hydrocortisone and ACTH unquestionably constitutes one of the major therapeutic advances attributable to their use.

* * *

The discovery and preparation of ACTH and the adrenocortical steroids has presented the medical profession with a potent and challenging group of new therapeutic agents. The important metabolic effects mediated by these hormonal preparations can only be appreciated fully by physicians who are prepared to devote time and effort to improving their understanding of the intermediary chemical reactions that permit man to adapt successfully to an ever-changing environment. Not only have these hormones provided specific substitution therapy and diagnostic aids in complex endocrinopathies but also their effectiveness in modifying the inflammatory response of tissues may ultimately increase understanding of the pathogenesis of many widespread and serious disorders. The successful use of hormone therapy in disorders other than the specific endocrine deficiencies requires careful judgment and the most effective application of the "art of healing." It is apparent that the ready availability of these hormonal preparations has presented the medical profession with a serious challenge, which is heightened by the intense interest of the general public in advances medical. It is hoped that the material presented in this review may provide a basis for increasing the usefulness of these substances as important pharmacologic agents.

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## MEDICAL INTELLIGENCE

# IDEAS OF EIGHTEENTH-CENTURY BRITISH MEDICAL WRITERS ABOUT ANXIETY*

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WAVERLEY AND BOSTON, MASSACHUSETTS

THE present era has been termed "the Age of Anxiety," because many believe that anxiety is now more widespread than ever before. As pointed out below, the characterization is valid only if it is taken to mean that there is an intense preoccupation with anxiety in the twentieth century. There is no evidence that severe anxiety is more commonly experienced today than in earlier times; indeed, it is probable that the Age of Anxiety began with Adam, or perhaps earlier.

A growing interest in anxiety as a symptom in emotional disorders was evident among Continental European writers of the late nineteenth century. At the end of that century the concepts of "anxiety psychosis" (in the writings of Wernicke) and "anxiety neurosis" (in the works of Hecker, Freud and Löwenfeld) were advanced. These developments were outlined in Forster's historical résumé, published in 1910. The diagnosis "anxiety psychosis" has largely been abandoned, but the concept persists in the term "agitated depression." In the present century the writings of Freud and his followers have led to the establishment of the idea that anxiety is at the core of mental and emotional disturbances; moreover, the importance of anxiety (or attempts to avoid it) is currently stressed not only in psychology but also in sociology and anthropology. It might be of interest, therefore, to study the role of anxiety as a symptom in the medical literature of a somewhat earlier period. Eighteenth-century British writings permit such a study, since they contain more regular mention of anxiety than those of Continental Europe do. There is another reason for studying the ideas about anxiety held by medical writers of that time: whereas the terms "hysteria," "hypochondriasis," "neurosis" and "conversion" were used differently then, — the last two completely so, — "anxiety" had the same meaning then as now. Occasionally, the words "inquietude" and "anguish" were employed as synonyms for "anxiety."

The seventeenth century saw the emergence of a modern concept of clinical medicine in England, as exemplified in the writings of Sydenham, Harris, Willis, Glisson, Lower and others. The influence of Sydenham was especially strong; his return to the practice of Hippocratic observation and his avoidance of complicated theory established the pattern of British medical thinking for succeeding centuries. The remarkable expansion of clinical observation that took place in England, Edinburgh and Dublin during the nineteenth century is well known; many of the syndromes and physical findings encountered in clinical medicine today still bear the names of great English, Scottish or Irish physicians of that period. This increase in knowledge of organic disease tended to overshadow interest in psychologic disorders.

The eighteenth century, on the other hand, was a period of transition, in that Sydenham's example was followed but the influence of ancient clinical observers remained strong. Discoveries in pathology had not yet brought about a division of medicine into diseases in which autopsy findings were definite and could be used to explain the symptoms (mainly diseases of blood vessels and of the abdominal and thoracic viscera) and diseases in which autopsy findings were vague or unremarkable (chiefly mental and emotional disorders). The writings of the great British clinicians of the eighteenth century treated mental and emotional disorders as fully as they discussed the conditions now regarded as belonging in the field of internal medicine. In addition, of course, some physicians devoted entire volumes to the separate consideration of mental diseases, and both Cheyne and Whytt wrote books on neurotic disorders per se.

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Conditions now considered forms of neurosis were then called "hypochondriac passion" and "hysteric passion." Sydenham, writing in the seventeenth century, believed both to be the same disease, and Cheyne, Heberden and others followed this teaching a century later. Some believed the two disorders to be "the male and female counterparts of each other." It should be noted that most physicians of that era recognized none of the difficulty in distinguishing hysteria from similar syndromes that is experienced by some modern authors. Brookes recorded the differential diagnosis as it was understood at the time; the hysteric passion was a paroxysmal disorder, whereas hypochondriac passion was a "tedious" disease, the manifestations of both conditions being somewhat similar. Even when the two conditions were believed to be separate, it was recognized that they were related. It was known that hysteric symptoms were sometimes observed in men and that the hysteric and hypochondriac syndromes commonly occurred in the same persons, either separately or concomitantly. It is possible that the modern introduction of the concept of conversion into the definition of hysteria has impaired a distinction between hysteria and other neurotic manifestations that seemed clear to physicians of earlier centuries.

Mead, following the earlier writings of Sydenham, expressed an idea held by most of his own contemporaries concerning the neurotic syndrome: "Non unam sedem habet, sed morbus totius corporis est." The many different somatic symptoms were described in the general medical writings of the eighteenth-century physicians Cullen, Ferriar, Heberden, Johnson and Macbride; in addition, they all listed anxiety as a manifestation of the hypochondriac disorder. Compendiums of extracts from the works of outstanding medical authorities were widely used at that time; that of Brookes, which was highly regarded, likewise stressed the occurrence of anxiety in the hypochondriac passion. In all these works the somatic manifestations of the disorder were described more fully than the emotional, but the authors indicated that anxiety was an important or, in some cases, the outstanding psychologic manifestation of the syndrome. Cheyne's book also emphasized the occurrence of ". . .apprehension and remorse. . .a perpetual anxiety and inquietude. . .a melancholy fright and panick, where my reason was of no use to me. . . ." Whytt, although he mentioned anxiety and other psychologic symptoms only briefly, referred to "fearfulness" as a principal symptom and noted "uneasiness not to be described."

Pinel reproached English (and German) writers on mental disorders for vagueness of description, for attachment to scholastic distinctions and for "producing mere compilations intermingled with a few scattered facts." These criticisms clearly apply to the writings of John Brown in England (and Stahl in Germany) and to a lesser extent to those of Mead, Parry and Rowley. These authors scarcely referred to symptoms at all, owing to their preoccupation with collection and classification — a preoccupation that apparently characterized all branches of eighteenth-century learning. On the other hand, the treatises on insanity written by Arnold, Battie, Burrows, Cox, Crichton, Haslam, Hill and Perfect do not deserve Pinel's reproaches. In all these writings anxiety was described as a regularly observed manifestation of hypochondriasis, which was referred to as a frequent precursor of melancholy. Arnold wrote a remarkable historical review of anxiety in melancholia, from Hippocrates and Aretaeus onward. In addition, all these writers emphasized the severity of the anxiety commonly noted in patients with psychotic depressions.

To these writers, the "constant internal anxiety" was a "principal symptom," "fixed," "habitual," "perpetual," "always personal," "groundless," "irrational," "delusive," "inexpressible" and "almost unbearable." The patients were "hypped and vapoured with imaginary or trifling evils." The anxiety was always described as attached to some real or imaginary environmental phenomenon; the concept of unattached anxiety did not appear in eighteenth-century discussions of the symptom, although the belief that anxiety might be primary was suggested by Macbride: "Anxiety excites the notion of some impending evil."

However thoroughly the eighteenth-century writers on mental and emotional disorders agreed on the importance of anxiety, they differed markedly regarding the causative mechanism. Cheyne believed that abnormal "gleiniess, syziness or viscidity" of the blood caused stasis everywhere and thereby precipitated the symptoms. Cadogan stated that nervousness in general was due to "an acid crudity of our fluids," thereby anticipating modern injunctions to "stay on the alkaline side." Others held that a "driving inward of the humors" was the mechanism — that the incarceration of blood in the abdominal and thoracic viscera caused the somatic complaints and that an excess of blood in the brain precipitated the psychologic disorder. Parry believed that increased pressure of blood in the brain was responsible.

However, there was still some uncertainty about the seats of emotions and feelings; some reference to their origin in the stomach or other organs can be found. On the other hand, all authors agreed on the more remote causes of the syndrome. Bodily constitution and injury were considered of great importance. The role of chronic illness was emphasized by Whytt: "There are few chronic distempers in which they [hypochondriac and hysteric symptoms] are not more or less blended or intermixed." He also observed that the visceral actions of the nervous system in neurotic adults were similar to those in normal children. Climatic conditions were

likewise regarded as important; Cox stated that some patients became "a sort of animated barometer." However, psychologic factors were held to be of the greatest importance in causing the illnesses in which anxiety was a symptom. These factors included the ordinary disappointments, fears and frustrations of everyday life and also other phenomena that were more subtle. Macbride observed that anxiety itself might be precipitated by "fear, grief, revenge and disappointment." Crichton regarded fear as "a modification of self-love" and described apprehension as often originating in mental associations. Battie extended the concept of anxiety to include all instinctual drives. He further said: "For uneasiness is so interwoven in the very frame of mortals, that even the greatest present satisfaction implies the removing or stifling the greatest uneasiness which before disquieted." This concept on the one hand reflects an ancient philosophy and on the other foreshadows a modern psychologic and sociologic belief.

References to a great increase in the incidence of mental and emotional disorders are found in the eighteenth-century works cited here. (Similar statements are common in the writings of all eras.) Haslam commented on the fact that physicians rarely encountered mild or early cases of mental disorders and accordingly had no accurate knowledge of their incidence. Cheyne stated (inaccurately) that the occurrence of neurotic disorders before his time was "scarce known to our ancestors and never rising to such fatal heights, nor affecting such numbers in any known nation. These disorders being computed to make almost one third of the complaints of the people of condition in England." Whytt found that neurosis was common in the poor country-people of North Britain. Cheyne entitled his treatise *The English Malady* (just as Beard, writing on neurotic disorders in America a century later, referred to them as "the American disease").

Cadogan wrote: ". . .every great degree of vexation, whether in the shape of anger, envy, resentment, discontent or sorrow, has most destructive and deleterious effects upon the vitals of the body, whether sudden or violent, or slow and lasting." Rowley noted specifically that neurotic disorders ". . .demonstrate clearly the surprising effects of the mind on the body." Whytt observed: "Nothing produces more sudden or surprising changes in the body than violent affections of the mind, whether these be excited by external objects, or by the exercise of internal sense." Interest in the somatic manifestations of emotion led to an enormous expansion of psychosomatic medicine in England in the early nineteenth century; this growth had no roots in physiologic observation and soon atrophied.

Although the medical writings of the eighteenth century contain references to the philosophic psychology of Berkeley, Hume and Hartley, this material proved to be of little value to British clinicians of that period. These physicians developed their appreciation of the importance of anxiety as a symptom through their own observations and through their study of the ancients — Hippocrates, Aretaeus and others. The belief that anxiety was actually the core of the problem of emotional disorder was the product of a later century and another region; it originated in the intuitive analyses of Continental writers rather than the extensive clinical observations of the eighteenth-century British physicians.

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# PSYCHOTHERAPY OF THE VULGAR WART

FEW pathologic processes have so challenged the therapeutic ingenuity of the medical profession as the lowly wart, *verruca vulgaris*, and probably no other infectious disease has been so enthusiastically recommended for psychotherapy. Certainly, there are few serious reports that the power of suggestion may be used to advantage to treat chicken pox, cold sores, cow pox or lymphogranuloma venereum,

but warts, as any schoolboy knows, have their metaphysical as well as their physical properties. No less dignified a publication than the *British Medical Journal* (and this in December, 1952) carries an account entitled "A Difficult Wart Treated by Suggestion."[1] Not only was an excellent result obtained — in a brass-turner — but also photographs taken before and after treatment of the finger provide positive proof that the wart actually did go away.

Because the process in this case involved the nail matrix, x-ray therapy was rejected, and the authors decided that "the only treatment that could possibly result in a *restitutio ad integrum* was to make the wart disappear by means of suggestion." So far, even the most skeptical will hardly disagree. The next step, of course, was to remove the wart by suggestion, especially since the patient was cooperative and in his own words "willing to try anything." It seems almost superfluous to add that six weeks later *restitutio ad integrum* was accomplished. Unfortunately, the case report terminates without description of the nature of the suggestive therapy.

Fortunately, however, the whole subject of suggestive therapy of warts is a matter of record, having been presented many years ago in a monograph by Twain[2] treating of the specific properties of *Felix Mortis, Aqua Spunki* and *Lentis Desiccans* as adjuvants to psychosomatic therapy:

"Say — what is dead cats good for, Huck?"

"Good for. Cure warts with."

"No! Is that so? I know something that's better."

"I bet you don't. What is it?"

"Why, spunk-water."

"Spunk-water! I wouldn't give a dern for spunk water."

"You wouldn't, wouldn't you? D'you ever try it?"

"No, I hain't. But Bob Tanner did."

". . .tell me how Bob Tanner done it, Huck."

"Why, he took and dipped his hand in a rotten stump where the rain water was."

"In the daytime?"

"Certainly."

"With his face to the stump?"

"Yes. Least I reckon so."

"Did he say anything?"

"I don't reckon he did. I don't know."

"Aha! Talk about trying to cure warts with spunk-water such a blame fool way as that! Why, that ain't a-going to do any good. You got to go all by yourself, to the middle of the woods, where you know there's a spunk-water stump, and just as it's midnight you back up against the stump and jam your hand in and say:

'Barley-corn, Barley-corn, injun-meal shorts,
Spunk-water, spunk-water, swaller these warts,'

and then walk away quick, eleven steps, with your eyes shut, and then turn around three times and walk home without speaking to anybody. Because if you speak the charm's busted."

"Well, that sounds like a good way; but that ain't the way Bob Tanner done."

"No, sir, you can bet he didn't, becuz he's the wartiest boy in this town; and he wouldn't have a wart on him if he'd knowed how to work spunk-water. I've took off thousands of warts off of my hands that way, Huck. I play with frogs so much that I've always got considerable many warts. Sometimes I take 'em off with a bean."

"Yes, bean's good. I've done that."

"Have you? What's your way?"

"You take and split the bean, and cut the wart so as to get some blood, and then you put the blood on one piece of the bean and take and dig a hole and bury it, 'bout midnight at the cross-roads in the dark of the moon, and then you burn up the rest of the bean. You see, that piece that's got the blood on it will keep drawing and drawing, trying to fetch the other piece to it, and so that helps the blood to draw the wart, and pretty soon off she comes."

"Yes, that's it, Huck — that's it; though when you're burying it if you say 'Down bean; off wart: come no more to bother me!' it's better. That's the way Joe Harper does, and he's been nearly to Coonville. . . ."

Such procedures and many others are mentioned in a recent review, by Allington,[3] of the psychotherapy of warts. "The reasons for spontaneous healing of warts," he observes, "are not known. . ." and he is frankly skeptical of methods such as "pressing or rubbing the wart with a piece of apple, pork or a pea and disposing of the material used by throwing it away or burying it," and even deprecates the value of burying a bean, half of which is covered with blood from the wart, at a crossroad at midnight in the dark of the moon.

These amateurish methods have apparently been outmoded by injections of sterile water, isotonic sodium chloride, an innocuous dose of bismuth or antibiotic or by exposure to an x-ray machine that emits noise instead of radiation. It comes as a refreshing surprise, therefore, to encounter a case of warts in a brass turner treated merely by unspecified suggestion, or to read of Bonjour's[4] method, which was to draw an outline of the wart in natural size, blindfold the patient and while touching the

wart lightly with a small ring or charm say (in French) "From today on you won't feel the warts any more and they will disappear." In some cases it was necessary to repeat the same procedure at monthly intervals. Although he presented no "actual statistics" Bonjour is reported not to have had a single failure in thirty years. (Actual statistics seem to be unnecessary in reports on the psychotherapy of warts.)

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### A READER'S PLEA

O editor dear, let me weep in your ear;
This sad thing has got to be said:
I cannot recognize, by shape or by size,
My old *New Eng. Journal of Med.*

It comes tattered and torn; it comes wrinkled and worn;
How it gets here, I cannot surmise,
For the postmaster chews it, and chomps it, and spews it,
And slaps it around, swatting flies.

Now, I read your apology for the *Journal's* pathology,
And your fiscal dilemma is plain,
But I'll never cease to bless that old crease,
If you'll just *wrap* the *Journal* again.

Why, bless that old wrapper! Quick open I'd snap 'er,
Always clean, always stout and intact.
The folding inside I could take in my stride —
Why, I even *liked* it, in fact!

So let my small voice influence your choice,
If choice there is ever to be.
For God's sake don't strap it, or flap it — *just wrap it!*
And send back my *Journal* to me!

R. M. Watrous, M.D.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

Benjamin Castleman, M.D., *Editor*

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### CASE 39151

#### Presentation of Case

A sixty-five-year-old widow entered the hospital because of dyspnea and anasarca.

Since the age of twelve the patient had had repeated attacks of "rheumatism" characterized by generalized pain and stiffness of the joints of the extremities, with questionable swelling and redness. The joints were involved simultaneously. The attacks lasted for two to six weeks and subsided without residual changes. The fifth and the last one occurred twenty years before admission. Ten years later she first experienced mild dyspnea and edema and had been on digitalis intermittently ever since. Eight or nine years before admission, she had sudden onset of heavy pain in the chest, without radiation. The pain lasted for at least half an hour and was relieved by injections; the patient was able to be up and around two or three days after this attack. No electrocardiogram was taken. In spite of the progressive dyspnea and intermittent ankle edema during the five years before admission, she was active until one year before entry, when the ankle edema became constant and after which she had led a bed-to-chair existence, walking only to meals and the bathroom. She received mercurial diuretics at first twice a week and later every other day, and ammonium chloride four days a week. Three months before admission, hypochloremia developed, and she became refractory to the mercurial diuretics. Since then, she had taken ammonium chloride every day, Neohydrin three times a day and Cystodigin, 0.2 mg. daily, and had been on a salt-free diet. During the past four months, her weight had increased from 156 to 190 pounds. Three months before admission, she spat up a tablespoonful of bright blood but had no chest pain, cough or increase of dyspnea, and was allegedly given 30 white pills "to prevent the blood from clotting." No blood test was done. She was never known to have had hypertension, liver disease, kidney disease or albuminuria. Cardiomegaly and apical systolic and diastolic murmurs were noticed five years before admission, when she was in another hospital.

Ten years before entry, a supracervical hysterectomy was performed because of a carcinoma of the uterine fundus, with removal of the cervix seventeen days later.

Physical examination revealed a chronically ill woman who was dyspneic at 90° position. The neck veins were distended and pulsating. There was a massive edema extending to the lower rib cage. The nail beds were slightly cyanotic. The chest was emphysematous, and rales were present over both bases, more on the left side. There was dullness at the right eighth and left ninth intercostal spaces, with egophony one space above. The heart was markedly enlarged, the left border extending beyond the anterior axillary line in the

fifth and sixth interspaces and the right border 3 cm. to the right of the sternum in the fourth space. The heart sounds were poor, and the rhythm was intermittently irregular. There was a Grade 3 apical systolic murmur and a questionable low-pitched apical diastolic murmur. No murmur was

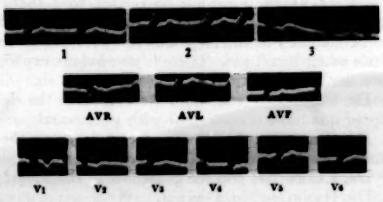


FIGURE 1.

heard at the base. The abdominal wall was edematous, and there was free fluid in the peritoneal cavity. The liver edge was felt 4 fingerbreadths below the

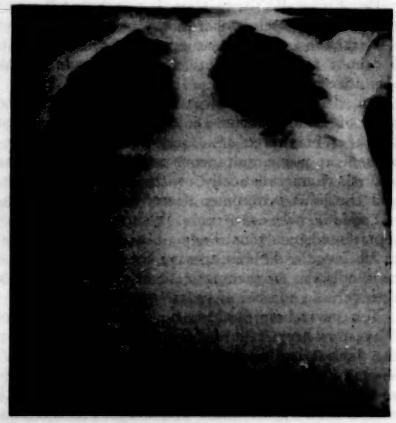

FIGURE 2.

costal margin; it was not pulsating. The spleen was not felt.

The temperature was 98.4°F., the pulse 80, and the respirations 27. The blood pressure was 90 systolic, 76 diastolic.

The urine had a specific gravity of 1.014 and gave a + reaction for albumin; the sediment contained rare granular casts and occasional white cells per high-power field. Examination of the blood disclosed a hemoglobin of 11.5 gm. and a white-cell count of 4400, with a normal differential. The blood sodium was 126 milliequiv., the potassium 5.2 milliequiv., the chloride 91 milliequiv., and the carbon dioxide 27 milliequiv. per liter; the non-protein nitrogen was 36 mg., the total protein 5.1 gm., the albumin 3.1 gm., the globulin 2.0 gm., and the bilirubin 0.4 mg. direct and 0.8 mg. total per 100 cc. The blood pH was 7.42, and the prothrombin time 15 seconds (normal, 13 seconds). The stool guaiac test was negative. An electrocardiogram showed auricular fibrillation with a rate of 65, a QRS interval of 0.16 second and normal voltage (Fig. 1). The R waves were slurred

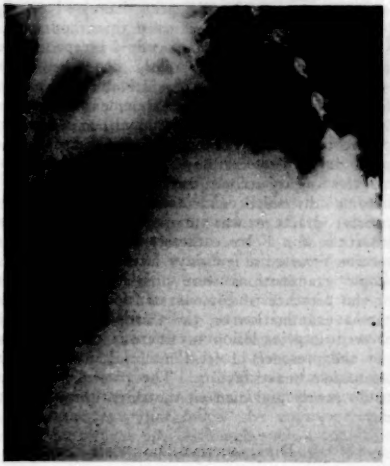

FIGURE 3. *Roentgenogram Showing Marked Cardiac Enlargement Anteriorly from Huge Dilatation of the Right Ventricle.*

in Leads 1, 2, AVR and AVL. $RR^1$ waves were present in Leads $V_1$, $V_2$, $V_3$, $V_4$, $V_5$ and $V_6$, and the S waves were slurred in Leads 1, 3, AVR, AVF, $V_4$, $V_5$ and $V_6$. There were ST-segment and T-wave changes secondary to the conduction defect. Roentgenograms of the chest demonstrated a gross enlargement of the heart to the right and the left (Fig. 2 and 3). There was fluid in the right side of the chest and almost certainly in the left.

On the second hospital day, 1700 cc. of straw-colored, clear fluid was removed from the abdomen, and 2100 cc. four days later. Southey tubes were inserted in the legs on the third day, 1800 cc. of fluid being drained out on the following day. In the meantime, the patient was given ammonium chloride and Mercuhydrin injections intravenously. In the following two and a half weeks, she lost 56

pounds. On the ninth day, she was observed to have increasing abdominal distention, with visible peristalsis and high-pitched tinkles with a few rushes. She had had no bowel movement for two and a half days and had passed no gas in twelve hours up to that time. The temperature, pulse and respirations were unchanged. Rectal examination was negative. A Levine tube was passed, and 350 cc. of thick, chocolate-colored material was aspirated from the stomach. An x-ray film of the abdomen revealed large distended loops of large bowel and some ill defined density in the right upper abdomen, probably gallstones. The blood chemical constituents remained at about the previous level except for the carbon dioxide, which was 18 milliequiv. per liter. The distention increased rapidly, and a cecostomy was performed three hours later. Liters of straw-colored ascitic fluid escaped during the operation, and the greatly distended cecum was decompressed. Postoperatively, the patient felt much better, and the abdomen was softer. Her general condition fluctuated, and she appeared to be slowly failing. On the twentieth hospital day, the cecostomy tube slipped out, and on the twenty-second day, the abdomen again became distended and the cecostomy drained poorly; drainage was temporarily improved by insertion of a Foley catheter, but abdominal distention recurred a few days later. Two sigmoidoscopic examinations were unsatisfactory because of the presence of copious soft feces. A barium-enema examination on the thirtieth hospital day showed no gross lesion anywhere in the colon, and yet the presence of fecal material made the examination unsatisfactory. The patient continued to do poorly and died on the thirty-third hospital day.

## Differential Diagnosis

Dr. Richard J. Clark*: May I see the x-ray films?

Dr. Joseph Hanelin: The heart, which is tremendously enlarged, fills up the greater portion of the thorax (Fig. 2). There might well be a huge right ventricle; at least the bulk of the cardiac enlargement extends anteriorly (Fig. 3). There is some fluid at either base, perhaps a greater amount on the left side.

Dr. Clark: Is there any suggestion of abnormal calcification?

Dr. Hanelin: I cannot see any cardiac calcification, but it could easily be missed in these films; it is generally picked up at fluoroscopy. The films of the abdomen, made at the time that the abdominal symptoms became severe, show a massive ascites and gross distention of the large bowel. This lateral film, made with the patient lying on her back, demonstrates multiple dilated loops of large bowel. The film after cecostomy and decompression of the bowel shows considerable lessening of colonic distention. A subsequent barium-enema examination discloses no obvious colonic obstruction, but the bowel contains a good deal of feces.

Dr. Clark: Would you be willing to make the statement that the intestinal obstruction, if there is one, is down low in the large bowel?

Dr. Hanelin: I cannot be certain that there is intestinal obstruction. Most of the distention seems to be confined to the large bowel, and there is very little small-bowel gas. There is no obvious explanation for the distention.

Dr. Clark: Do you think the shadow in the right upper quadrant is consistent with gallstones?

Dr. Hanelin: I cannot be certain from these films.

Dr. Clark: Do you see gallstones in the colon?

Dr. Hanelin: No; I do not.

Dr. Clark: There are several other facts that I should be interested in knowing. At the time when what was apparently acute intestinal obstruction developed, what was the white-cell count? Was a pelvic examination done in addition to the rectal examination? Do we know whether both ovaries were removed at the time of the operation?

Dr. Edgar B. Taft: There is no white-cell count recorded. The pelvic operation was done at another hospital, and we have no specific report about it. I cannot find evidence that a pelvic examination was done here.

Dr. Clark: This patient had five attacks of some type of rheumatic or joint involvement between the ages of twelve and forty-five. The joint involvement was simultaneous and not migratory as occurs characteristically with rheumatic fever, and the joint symptoms cleared completely, without residua, between attacks. Whether these episodes represented recurrent rheumatoid arthritis or rheumatic fever is difficult to say; they may well have been episodes of rheumatic fever extending over a considerable number of years.

Ten years before admission, there was onset of congestive heart failure. Then a year or two later, the patient had an episode of "heavy chest pain." We may wonder about the possibility that this pain was caused by coronary-artery disease but with only 1 such attack noted and with no further confirmatory evidence, I should think it was more likely to have been caused by pulmonary disease, possibly infarction. Five years before admission she presented a murmur suggestive of mitral stenosis and regurgitation. The dyspnea was progressive, and one year before admission, the intermittent ankle edema became more severe. At that time she became refractory to mercurial diuretics. That not infrequently occurs in people with cardiac disease whose sodium intake has been strictly restricted and who have received large amounts of mercury. Thereafter she was given Neohydrin, an oral preparation of Mercuhydrin that has been

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moderately effective in some patients. Most physicians would agree, I think, that when Mercuhydrin is ineffective by injection, mercury by mouth is rarely effective. At any rate, in spite of the mercurial diuretics, increasingly severe congestive heart failure developed. She also had an episode of hemoptysis, which the physicians taking care of her evidently thought was caused by pulmonary infarction since they gave her Dicumarol. Whether the hemoptysis was the result of pulmonary infarction or of severe pulmonary congestion, I cannot be sure, although I should have expected more palpitation and an increase in the dyspnea with pulmonary congestion.

In the hospital the laboratory tests revealed a urinalysis consistent with the kidneys of congestive heart failure. The blood sodium and chloride were significantly lowered. The electrocardiogram indicated a high degree of right-bundle-branch block and suggested that the right ventricle extended well across the entire anterior precordium, with its complexes extending through Lead $V_5$.

The patient again responded to mercurial diuretics in spite of the low sodium and low blood chloride content; this may occur after a temporary rest from mercurial diuretics. Response to diuretics is often improved after paracentesis. In two and a half weeks she lost 56 pounds, more than she had gained in the previous four months.

It is almost certain that this patient had rheumatic heart disease. I do not believe that any other type of heart disease would fit this picture and history. She had no hypertension and no hypertensive heart disease; I am not willing to accept coronary-artery disease; there is no lead in the history to point toward a congenital heart lesion. She had some emphysema, but certainly, if she had had a cor pulmonale, she would have had more respiratory symptoms, and when failure set in she would have had a much more rapidly fatal course. The question of chronic adhesive pericarditis must be considered, but I should not have expected a course such as this, or such a large heart, and I should have expected evidence of pericardial calcium by x-ray examination. The bizarre ill defined types of chronic myocarditis, of which we have seen an increasing number in recent years, may mimic the severe adhesive pericardial disease and may produce severe, unremitting congestive heart failure, sometimes of the degree noted in this patient. This diagnosis rests largely on exclusion of other etiologic factors, and I shall exclude it here because of the evidence for rheumatic carditis.

Since I have assumed that rheumatic heart disease was present, what valves were involved? I can make no definite diagnosis of valvular disease except mitral stenosis and regurgitation. The tremendous size and the configuration of the heart in the x-ray films are compatible with these lesions. No basal murmurs were noted to suggest aortic-valve disease. Tricuspid regurgitation certainly should be considered in view of the gross failure and the marked ascites, but the strongest argument against it is the absence of a pulsating liver. The autopsy may have given evidence of old pulmonary infarction.

Evidently, the Services considered that this patient had an acute intestinal obstruction. The onset of the picture in the abdomen was a little unusual; no pain was noted. There was no change in the chart. There was a gradual rather than an abrupt dramatic onset. Did she have an intestinal obstruction? There certainly was evidence of it. If there was obstruction, I think that it was in the large bowel and not in the small bowel. When a patient with cardiovascular disease has an acute intestinal episode of this sort, one thinks of mesenteric embolism or mesenteric thrombosis. Certainly, this patient had a setup in which either of these conditions could well have occurred. However, there are several things that bother me. In the first place with mesenteric embolus or thrombosis, the obstruction much more commonly involves the small bowel, for which there is little evidence in the case under discussion; mesenteric embolization to the large bowel usually has to be extensive to produce obstruction since there is such widespread collateral circulation in the colon. If this patient had had a massive vascular accident to the large bowel, she should have had a far more dramatic course, with a high white-cell count — although I do not know what the white-cell count was — and evidence of bleeding either from the large bowel or into the abdomen. There was no serosanguineous abdominal fluid, and the stool examination showed no blood. The diagnosis of mesenteric thrombosis is frequently missed. It can be extremely illusive, and may not follow the commonly described pattern at all. Although such a condition may well have existed in this case, I do not believe that there is sufficient evidence on which to make this diagnosis.

Obviously, the Service was looking for an intrinsic bowel lesion or some other source of obstruction. This woman had carcinoma of the uterus ten years before admission. I am told by the gynecologists that recurrence of a carcinoma after ten years is unusual. This patient may well have had malignant recurrence in the pelvis that extrinsically compressed the bowel and may even have been a factor in the massive ascites. Moreover, if an ovary had been left behind, cancer developing in this could very well have produced the entire picture. These can only be mentioned as possibilities without any evidence for them on pelvic examination. An intrinsic lesion, a carcinoma or a polyp in the colon, could not be found on examination, but the examinations admittedly were unsatisfactory. I cannot exclude any of these possible factors; yet we have no proof for any one of them. I wondered for a moment if a gallstone could

have caused the obstruction, but evidence for that is too fragmentary. I do not know what was causing intestinal obstruction in this patient. I shall not be surprised to learn that the pathologist did not find any cause for it. We know that patients with massive ascites, particularly patients who have been tapped, may have surprising and bizarre gastrointestinal-tract symptoms. I suspect that the pathologist found evidence only of massive congestion and ascites in the abdomen.

I shall rest the case with the diagnosis of rheumatic heart disease, severe mitral stenosis and regurgitation and massive congestive heart failure, with old pulmonary infarction.

DR. S. M. KRANE: I think there are a few points to be cleared up about the clinical course. The murmur in the apex was definitely heard and was thought to be a Grade 2 rumbling mid-diastolic murmur. The neck veins were never distended, but there was a marked deep systolic jugular pulse. Even if there had been a pulsating liver it could not have been felt because of the ascites and the distention of the abdomen. The onset of intestinal obstruction seemed to occur rapidly over a period of several hours even though the patient was already distended. The dilatation was quite striking over a short period. Another point is that while she was on the Surgical Service, the surgeons kept removing impacted feces from the bowel but never could demonstrate any lesion.

DR. JAMES H. CURRENS: The electrocardiogram is most unusual for uncomplicated rheumatic heart disease. I was wondering if Dr. Clark would consider the possibility of a defect of the atrial septum to account for the high degree of impairment of intraventricular conduction? This recently proved to be an important clinical observation in a patient who did have an atrial defect.[1]

DR. CLARK: That is a very good thought; certainly the x-ray findings were consistent with a Lutembacher syndrome — a defect of the atrial septum combined with mitral stenosis.

DR. TAFT: I should like to ask Dr. Hanelin if he does not think the lungs are unusually clear in this x-ray film with all this cardiac dilatation.

DR. HANELIN: Yes; I think so. There is not the usual texture of the lung that we see with long-standing pure mitral stenosis. Some of the vessels that are shown — many of them are obscured by the heart itself — look somewhat enlarged in the lower portion of the lung field, and there is a bilateral pleural effusion, which goes with some degree of congestive pulmonary change.

### CLINICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis and auricular fibrillation.
Congestive heart failure.
Fecal impaction.
Cecostomy.

### DR. RICHARD J. CLARK'S DIAGNOSES

Rheumatic heart disease, with severe mitral stenosis and regurgitation.
Massive congestive heart failure.
Old pulmonary infarction.

### ANATOMICAL DIAGNOSES

*Rheumatic heart disease, with chronic endocarditis, inactive, of all valves.*
*Pulmonary stenosis, rheumatic, with marked right-sided cardiac dilatation and hypertrophy.*
Anomalous pulmonic valve (4 cusps).
Cardiac failure, evidenced by bilateral hydrothorax and ascites, cardiac cirrhosis of liver and chronic passive congestion of spleen and kidneys.
Coronary-artery disease, mild, with old myocardial infarction, left ventricle.
Pulmonary infarcts, small.
(Fecal impaction.)

### PATHOLOGICAL DISCUSSION

DR. TAFT: The pelvic organs, including the ovaries, were absent. The large bowel at the time of autopsy was filled with soft feces and gas. There was no evidence of obstruction although two small polyps were found in the hepatic flexure and one in the sigmoid. The marked evidence of heart failure that was seen on the ward had disappeared. There was only a small amount of pleural fluid and ascites and no peripheral edema. The lungs, except for two small infarcts, were not remarkable. There was chronic passive congestion of the spleen, kidneys and liver, and in the liver there was a moderate amount of increased fibrous tissue, particularly beneath the capsule and in the perilobular hepatic veins, which was consistent with repeated bouts of heart failure.

The heart was the most interesting organ, as might have been suspected. It was enormously dilated, weighing 770 gm. The right ventricle had a capacity of 550 cc., the right atrium one of 400 cc., the left atrium one of 200 cc., and the left ventricle one of 120 cc. The right ventricle measured 6 mm. in thickness so even in its state of marked dilatation it was thicker than usual; the left was of the usual thickness. In the apex of the left ventricle there was a marked thinning of the wall with gray-white fibers, which looked very much like the picture we see with an old infarct, but we could not demonstrate any occlusion in the coronary vessels leading to that area. The endocardium was thickened in areas, but there were no mural thrombi in any of the chambers of the heart. All four valves were involved with an old rheumatic process. The mitral valve and the tricuspid valve had thickened leaflets, and the chordae tendineae of each were thickened and shortened, which is good evidence of rheumatic involvement of these valves. There

was interadherence of the cusps of the aortic valve, with thickened edges and mild stenosis. The pulmonic valve was anomalous as well as being involved with the rheumatic process. There were four cusps. The extra cusp was much smaller than the others — about one third their size. There was marked interadherence of the cusp leaflets, with stenosis and reduction of valvular lumen, although the valve did not appear to be incompetent. Microscopically, the valve cusps were somewhat cellular. There were no areas of perivascular inflammatory-cell infiltration or of Aschoff bodies in the cardiac muscle.

We are therefore left with the problem of explaining the enormous dilatation of this patient's heart, particularly the right side, and her long survival with such relatively extensive heart disease. I am sorry that Dr. Paul D. White could not be here today to give us his opinion. From his discussion of multiple valvular lesions in his book on heart disease,[2] it seems that the old concept that patients with multiple valvular involvement tend to live longer is incorrect. The best explanation of this patient's long survival may therefore be that although all heart valves were involved, none were functionally impaired to more than a moderate extent, with the possible exception of the pulmonic valve. And it is in this unusual and marked involvement of the pulmonic valve that we find the explanation for the tremendous enlargement of the right ventricle. Dr. White remarks that the most severe enlargement of this side of the heart accompanies stenosis of the pulmonic valve.

DR. CURRENS: Were the coronary arteries abnormal?

DR. TAFT: There was slight involvement with atherosclerosis.

DR. CLARK: Did anybody who saw the patient describe a basal murmur at any time?

DR. KRANE: We were never able to hear any sounds at the base at all except the systolic murmur.

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1. Case Records of the Massachusetts General Hospital (Case 38481). *New Eng. J. Med.* 247:852-857, 1952.
2. White, P. D. *Heart Disease.* 1015 pp. New York: Macmillan, 1951. P. 700.

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## CASE 39152

### PRESENTATION OF CASE

A sixty-year-old married woman was admitted to the hospital complaining of pain in the left lower quadrant.

For a year or more the patient had had an occasional dull pain in the left or right lower quadrant. Two days before admission a dull pain in the left lower quadrant suddenly occurred, subsiding in an hour or so. This dull pain recurred from time to time on the day before admission, but six hours before admission there was a sudden onset of a sharp, severe pain in the left lower quadrant, and this severe pain, though intermittent, persisted. It was accompanied by slight nausea, but no vomiting. Slight urinary frequency was noted, but no burning or hematuria.

At no time had the patient noticed hematemesis, pain before or after meals, intolerance of any food, melena, diarrhea, jaundice or chills. There had been no postmenopausal bleeding.

On examination, the patient was in acute distress, rolling about in bed. The heart was not enlarged, no murmurs were heard, and the aortic second sound was louder than the pulmonic. The chest was normal. There was no costovertebral-angle tenderness. Examination of the abdomen showed no tenderness except in the lower portion, where there was slight tenderness and vague sensation of a mass arising above the symphysis pubis. Pelvic examination revealed a mass that nearly filled the pelvis, irregular in outline and tender on the left side. Rectal examination confirmed this finding.

The temperature was 98.4°F., the pulse rate 80, and the respirations 20. The blood pressure was 185 systolic, 90 diastolic.

The hemoglobin was 14.0 gm. per 100 cc., and the white-cell count 9500, with 83 per cent mature and 1 per cent young neutrophils, 15 per cent lymphocytes and 1 per cent monocytes. The prothrombin time was 13 seconds (normal, 13 seconds). A plain film of the abdomen showed a number of small calcifications consistent with gallstones. There was a small area of calcification to the left of the third lumbar vertebra, but this appeared to lie anterior to and outside the urinary passages. A vague soft-tissue fullness lay over the left wing of the sacrum, but no definite mass could be outlined. A barium-enema examination revealed no intrinsic abnormality, compression or displacement, the barium flowing easily to the splenic flexure. The examination was voluntarily discontinued at this point.

On the second hospital day, sixteen hours after admission, an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. ROBERT S. SHAW*: This sixty-year-old woman entered the hospital with a pelvic mass; presumably, she had some condition in the lower abdomen or pelvis for a year or more and had an acute process in this region that brought her to the hospital. The differential diagnoses include congenital, inflammatory and neoplastic lesions. In this age group it is not likely to have been a congenital lesion. It was probably not an inflammatory lesion since she had no fever and no marked elevation of the white-cell count although there was apparently elevation in the percentage of neutrophils.

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Where could this lesion have arisen? It could have been a process arising in the sigmoid, but this was ruled out by a barium-enema examination. It could have been in the urinary tract. Although I am not given a report of the urinalysis, I think we can assume it was done, and that it was not contributory. Moreover, it is routine to catheterize patients of this sort on admission so I can assume that the mass did not disappear with catheterization. This mass, then, was in the uterus or the adnexa. I am not told whether on physical examination the uterus was related to this mass, but with symptoms that lateralize, it probably arose in the left adnexa. Certainly the most common tumor in the adnexa is an ovarian tumor. That narrows the choice to a consideration of ovarian tumors.

This patient had a tumor for a year or more, with symptoms from its physical presence alone; then she had an acute accident that brought her to the hospital. There are two possible explanations, one being torsion and the other leakage or rupture of an ovarian cyst. It is unlikely that there was leakage or rupture, for there were no symptoms or signs of peritoneal irritation. Certainly, the history was characteristic of torsion or twist of an ovarian tumor. Probably a few days before the day of admission she had a partial torsion of the tumor that was not marked enough to cause severe symptoms; then, on the day of admission, she had more complete torsion with quite characteristic symptoms. The urinary frequency was certainly due to the presence of the mass and not to any intrinsic disease of the urinary tract. The slight nausea that she had is also consistent with a twisted ovarian tumor. The pain that she had did lateralize to one side; therefore, I think I can say the lesion was a twisted left ovarian tumor.

I might discuss the various sorts of ovarian tumor to try to narrow the diagnosis down more. In the films there was calcification arising in the left side, which was the probable side of the lesion; however, the calcification seems to have been high, at the level of the third lumbar vertebra. Perhaps this is a good time to look at the x-ray films. If the calcification was in the tumor, they would certainly be of help.

Dr. Stanley M. Wyman: The calcifications, which are very numerous, are consistent with gallstones in the right upper quadrant. The calcification that Dr. Shaw spoke of lies to the left of the transverse process of the third lumbar vertebra, moves in relation to the kidney and seems to lie too high to be in the soft-tissue fullness described in the left lower abdomen. This fullness is seen overlying the left sacrum and left pelvis although it could not be outlined as a discrete mass. The films selected from the barium-enema examination demonstrate a normal lower colon. The examination was discontinued because the information required was only about this portion of the bowel. The lower colon is not appreciably displaced or compressed.

Dr. Shaw: Of the tumors of the ovary, the first to be considered are the benign, cystic ones; that includes the follicle non-neoplastic cysts, the lutein cysts and the endometriomas — the last are almost entirely in the younger age group so we can disregard them. An inflammatory cyst would be unlikely without a previous history or signs and symptoms of inflammatory disease. Pseudomucinous cystadenomas certainly can be as large as or much larger than the mass described. They are reported as being rare in patients above the age of sixty so whereas initially this diagnosis seemed reasonable, I shall have to put it low on the list. Dermoid cysts and teratomas usually occur in patients between twenty and thirty years of age, but they may occur in any age group. Also, they are prone to twist, having a very long pedicle and only occasionally being adherent to the pelvic peritoneum. I think this is a fair possibility. It would be very pleasant to have a large tooth visualized in the left pelvis, but I am not blessed with that.

Among the solid benign tumors that I have to consider is fibroma. That tumor characteristically occurs in old people. The ones that we have seen have been smaller than the tumor in the case under discussion and are characteristically hard, feeling like a uterine fibroid. I think that if this sort of tumor was felt it would have been noted. Such tumors are occasionally associated with ascites and hydrothorax (Meigs' syndrome). They also are prone to twist, having a narrow pedicle. I do not have to consider that as seriously as a dermoid cyst or teratoma. Another lesion that may be solid or partially cystic is a Brenner tumor, which also occurs in older patients. It does not have any specific characteristics by which we can recognize it clinically. It may be but is not necessarily associated with ascites. This is a relatively rare tumor, and for that reason I do not think I shall consider it too seriously.

Among the malignant tumors the first one to consider is an ovarian carcinoma. This patient, as far as her age is concerned, was right at the peak of the incidence. The most common ovarian carcinoma in this hospital is a papillary serous adenocarcinoma. These tumors are not likely to become twisted because they usually have broad pedicles and become adherent to the pelvic peritoneum. Wheelock et al.[1] looked up these cases in this hos-

pital several years ago and found that among 67 cases there was no incidence of a twisted pedicle. However, early in their development the tumors may be free, and it is conceivable that then an ovarian carcinoma could become twisted. These tumors are quite malignant and may grow rapidly, but there are cases of women living many years with known ovarian carcinomas. I am not sure on the basis of the long history and symptoms that I can rule it in or out. Ovarian sarcoma is excluded because it is almost entirely confined to the younger age group. I cannot make a diagnosis of metastatic ovarian tumor because of the complete absence of anything in the systemic review or physical examination suggesting a primary tumor elsewhere.

The functioning ovarian tumors — the granulosa-cell tumor, the thecal-cell tumor, the luteoma and the arrhenoblastoma — I do not believe I am justified in considering because there was no evidence of estrinization, no vaginal bleeding and no description of virulism. Dysgerminoma is also considered to be functioning because it gives rise to positive urinary Aschheim–Zondek tests; however, it occurs in the younger age group and is quite rare.

I do not think that I am justified in naming a particular type of ovarian tumor; I can only say that the patient had a twisted left ovarian tumor, certainly neoplastic and probably benign — at least benign in the sense that it could be cured by surgery.

### Clinical Diagnosis

?Twisted fibroid.

?Ovarian tumor, with twisted pedicle.

### Dr. Robert S. Shaw's Diagnosis

Twisted left ovarian tumor, benign.

### Anatomical Diagnoses

*Twisted left salpinx, with infarction of left ovarian fibroma.*

Bilateral ovarian fibromas.

### Pathological Discussion

Dr. Robert H. Fennell, Jr.: This patient was operated on by Dr. Claude E. Welch, whose preoperative diagnosis was twisted uterine fibroid or ovarian tumor with twisted pedicle. At operation the patient had bilateral ovarian tumors, a large, pale tumor on the right and a large hemorrhagic tumor on the left, both of which were removed with the tubes and uterus. There was no ascitic fluid. We received the specimen in the laboratory as two ovarian tumors both approximately 8 cm. in diameter. The right one was pale and hard, and a small, clear cyst was present on the surface. The left tumor was similar but was dark red, almost black, and obviously partially infarcted. The left tube was also partially infarcted. The twist had occurred in the midportion of the tube, and one could definitely determine this area by the abrupt transition from normal to hemorrhagic tissue. Histologically, these tumors were fibromas, made up of orderly arranged spindle-shaped cells with interspersed dense bands of collagen. The uterus was small, and the endometrium was thin and atrophic.

Dr. W. R. Owens: Do fibromas often occur bilaterally?

Dr. Fennell: Yes; in about 10 per cent of the cases that Dockerty and Masson[2] reviewed.

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2. Dockerty, M. B., and Masson, J. C. Ovarian fibromas: clinical and pathologic study of 283 cases. *Am. J. Obstet.* 47:741-752, 1944.

**Evaluation of Clinicopathological Exercises.** To evaluate the place of the clinicopathological conference in medical education, Dr. Castleman would like to obtain a list of the groups that use the Case Records of the Massachusetts General Hospital as a teaching exercise in their society or hospital meetings, dinner clubs, student conferences and so forth. If it becomes practical, would your group be interested in obtaining pertinent lantern slides of roentgenograms, specimens and so forth with each case? Replies indicating the method used in the group should be made directly to Dr. Castleman, Massachusetts General Hospital, Boston 14. Comments and suggestions will be welcome.

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## REGARDING ANXIETY

THE definition of anxiety as "a painful uneasiness of mind over an impending or anticipated ill" has given rise to a modern interpretation of St. Matthew's familiar verse (6:27), "Which of you by *bring anxious* can add one cubit unto his stature?" The idea suggests the antiquity of this so-called modern curse of men and of nations; indeed, Altschule, in his philosophical essay on "Ideas of Eighteenth Century British Medical Writers Regarding Anxiety," published elsewhere in this issue of the *Journal*, expresses the probability that the Age of Anxiety began with Adam, if not earlier. It is, in fact, more than possible that the serpent, in enticing Eve, was ventilating his own feelings of insecurity and of guilt, derived from the Tree of Knowledge, which he was supposed to be guarding. Recently Terhune, in the February, 1953 issue of GP has aptly identified anxiety as the hyphen between "psycho" and "somatic."

There is nothing new under the sun. King James, it appears — either I or II — is credited with having been an authority, in his time, on peptic ulcer, and Altschule demonstrates most convincingly the important part that an interpretation of the anxiety syndrome played in the medical thinking and the medical literature of the period of which he writes.

George Cheyne, the physician of Bath whose name the founder of the Shattuck lectureship of the Massachusetts Medical Society bore, described the syndrome most convincingly in 1733 as the "English Malady" — "a melancholy fright and panick, where my reason was of no use to me. . . ." Altschule quotes also from Battie, who, twenty-five years later, came close to a concept of the basic cause of this curious incapacity: "The uneasiness is so interwoven in the very frame of mortals, that even the greatest present satisfaction implies the removing or stifling the greatest uneasiness which before disquieted."

Even as knowledge, however, or the capacity to enlarge on one's frustrations, real or imagined, is the basis of that anxiety in which all mortals share, so knowledge and directed understanding are the only tools by which it can be measured; the only weapons by which it can be overcome or held at bay.

The danger is that this defensive mechanism of anxiety instead of functioning to the limit of its normal, protective value and then being met head on, as a problem of living, and brought under control will continue to be used as pseudoscientific sales talk for a variety of sedatives.

Uneasiness is the penalty of possessing the capacity to appreciate and magnify all the disturbing factors in a competitive and not altogether friendly environment. It may be temporarily abated with bromides and barbiturates, but it can be controlled only through the exercise of the fortitude that comes with understanding. It is not limited to those who must assume great responsibility. Lesser mortals,

with their limited responsibilities, can suffer from it as well. As Hoffenstein so elegantly expressed it:

The head that wears a crown may be
Inclined to some anxiety,
But, on the other hand, I know
A derby domes its meed of woe.

## TREATMENT OF PLANTAR WARTS

The disability that can be caused by plantar warts is most evident to the medical officer caring for the foot soldier. Unlike warts elsewhere, plantar warts, because of their deep location in the stratum germinativum of the skin of the feet, are capable of causing incapacitating pain out of all proportion to their size. Moreover, they occasionally increase in size to cover so large an area that surgical treatment is both expensive and unduly prolonged — so much so that during World War II it was actually more expedient to reclassify some troops all the way back to the Zone of the Interior from Africa, Italy or England than to attempt definitive cure in military installations abroad. Thus, attempts such as that recorded elsewhere by Branson in this issue of the *Journal* to treat plantar warts early and with as little disability as possible warrant testing by others. Probably more should be done than is done toward prevention instead of cure of warts, but until the epidemiology is further clarified, emphasis must remain on early clinical detection and early cure. In military life such detection can be accomplished easily as a refinement of "short-arm" inspection, which presumably includes, in addition to its venereologic implication a search for crab lice, body lice, scabies, trichophytosis, chiggers, mites and various other microbiologic bedfellows.

Branson's method of cure is to inject 2 or 3 cc. of 1 per cent novocain under pressure (using a dental syringe) into the base of the wart, with the bevel of the needle reaching at an angle into the stratum germinativum. If the needle is properly placed, considerable resistance is encountered, bleaching of the skin is seen, and actual elevation of the wart is ultimately effected. Among 30 patients so treated 22 were cured before six months had passed. This rate is far from perfect but the fact that it was accomplished without change in the patients' duty status is noteworthy. The results suggest that it is not necessary to destroy every trace of verrucous tissue so long as the whole growth is critically disturbed and elevated.

Explanation for the success of the method is not clear, and Branson suggests that cure is due to ischemic necrosis of the wart; good results did not occur unless marked blanching, in addition to the elevation of the wart itself from the injection, was obtained. Branson also found that the novocain had no therapeutic action but was simply an analgesic. If this is so his suggestion of ischemic necrosis is reasonable; those who treat warts are familiar with the pin-point spots of hemorrhage characterizing the vascular core that emerges when the overlying callus is pared down to skin level. Surely, injection of a relatively large amount of fluid at the proper site — the junction of the verruca and the stratum germinativum — must result in avulsion of the wart, the base of which, in contrast to its apex, is soft and friable. The procedure used is well worth critical study, for if the efficacy of the method is confirmed and perhaps perfected, it may prove the therapeutic procedure of choice. The one technical maneuver that might prove most difficult would be to locate the base — perhaps erring on the high side rather than plunging the needle's bevel ineffectually into the corium.

## DIAMOND JUBILEE

The Diamond Jubilee of Medical Progress will be held in Richmond, Virginia, April 23 to 25 this year at the season, it is expected, when the woodbine spices are wafted abroad and the rose's musk is blown.

Intricately interwoven in the general celebration will be the First Western Hemisphere Conference of the World Medical Association and the Pan American Medical Confederation, which will hold their sessions at Medical College of Virginia on April 24; and the seventy-fifth anniversary of A. H. Robins Company, Incorporated, the ethical pharmaceutical house that was founded in Virginia in 1878 and is underwriting the expenses of the conference, the guests and the delegates.

Dr. Louis H. Bauer, president of the American Medical Association and secretary-general of the World Medical Association, will preside over the sessions at the Medical College, in which Dr. James

S. Simmons, dean of the Harvard School of Public Health, will participate.

In addition to the scientific and clinical discussions, special tours will pass through Richmond, stopping at St. John's Church, where Patrick Henry delivered his famous ultimatum. On the last day of the conference historic Williamsburg will be the principal point of interest.

As an appropriate gesture in observance of the lengthening of life and the constant improvement of health, Governor John S. Battle of Virginia has requested each of his 47 gubernatorial colleagues to appoint a physician who will reach the age of seventy-five during 1953 to visit the conference and tell of medical advances that have taken place during his lifetime. Since the lives of these 47 physicians will have been virtually coetaneous, various modifications of the same general theme are to be expected.

From northern New England Maine will be represented by Dr. George L. Pratt, of Farmington, New Hampshire by Dr. James W. Jameson, of Concord, Vermont by Dr. Stillman P. Grant, of East Dorset, and Massachusetts by Dr. James W. Sever, of Winchester. In the midst of a sincere appreciation of seventy-five years of pharmaceutical effort, it is expected that the virtues of *Mentha julapium* will not be neglected.

## CANCER CAMPAIGN

The annual campaign of the Massachusetts Division of the American Cancer Society, which will continue through the month of April, cites efforts made to achieve the objectives of the Society and stresses the challenge to be met in the future. In the belief that the most effective approach to eventual control of cancer is through research, education and service, the Division last year set aside $150,000 to support projects based on these objectives. The campaign this year stresses the need for even more funds for research and education and for the care of indigent patients with cancer.

The most significant contribution of the Division in 1951-1952 was to medical and statistical research and professional education, a total of $91,000 being allocated for this purpose. Specific projects included studies of factors that lead to inheritance characteristics, palliative effects of sex hormones and chemotherapy on some types of cancer, building up and breaking down of tissues and the action by which a certain virus inhibits cancer in mice. In Massachusetts, where there are 25,000 cases of cancer each year and where some of the world's greatest centers of cancer research are concentrated, grants-in-aid were liberally awarded to several large institutions.

Education of the public through every available medium, with co-ordination of many projects, continued throughout the year in an effort to persuade people to seek medical advice when signs or symptoms of cancer appear. The Division's education unit worked through schools, industrial concerns, clubs and organizations, by means of motion-picture films, exhibits, displays, information centers and every other available medium of mass information. Through local communities 38 per cent more people are now being reached than in previous years.

It has been estimated that 1 in 4 patients with cancer in the Commonwealth are needy. Since it is impossible to meet the demands of all such cases, the Division concentrates on those in greatest need, awarding grants principally to institutions caring for such patients and provided with local service departments. Such funds make possible home nursing care, certain appliances, special therapy and other direct help.

The growing challenge of cancer demands constant efforts to discover the cause and the cure. A few figures illustrate the gravity of the problem and the immediacy of the need for a solution. The disease is second among the leading causes of death (1 out of 7 deaths in 1951 were from this cause), accounting for more than seven times as many deaths as tuberculosis. It has been estimated that 22,000,000 people now alive will die of cancer unless new cures or preventive measures are discovered. The research sponsored by the American Cancer Society continues unceasingly in the form of projects designed to find both the cause and the cure, or cures, of the disease.

These projects, which represent the only available efforts at control, depend in large part on the funds raised by the American Cancer Society. Doctors are particularly urged to respond gener-

ously to the April appeal of the Massachusetts Division for sufficient contributions to enable these vital projects of research, education and service to continue.

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*Female colleges were denounced at a meeting of divines and others, at Pittsfield, Mass., the other day. They object to these modern institutions for turning women into men.*

Boston M. & S. J. *April 13, 1853*

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## MASSACHUSETTS MEDICAL SOCIETY

### EXECUTIVE COMMITTEE

The next meeting of the Executive Committee will be held at the Harvard Club, Boston, on Wednesday, April 22. The luncheon will be at 12 noon, and the meeting will follow at 1 p.m.

### TREASURER'S REPORT COVERING REFUND DISTRIBUTION

The Committee on Finance has voted to distribute the sum of $4,000 to the district societies for the year 1953. The total number of payments received by March 1, in time to count for the refund, was 4443, making the refund for each paid member $0.9003.

The following table gives the number of payments as of March 1 from each district, and the numerical change from last year's figures. Although the total amount of the refund is the same, the proportionate return to each district is influenced by the district's relative performance. A careful perusal of variations from last year may stimulate a sporting competition between the members of the districts next year to better their showing before March 1.

The actual amount of the refund to each district is shown as of March 20, 1953.

| District | No. Reported Paid | Refund |
|---|---|---|
| | | $ |
| Barnstable | 34 (down 5) | 30.61 |
| Berkshire | 133 (up 9) | 119.74 |
| Bristol North | 59 (down 12) | 53.12 |
| Bristol South | 201 (up 9) | 180.96 |
| Essex North | 168 (down 2) | 151.25 |
| Essex South | 244 (down 2) | 219.67 |
| Franklin | 38 (down 2) | 34.21 |
| Hampden | 322 (down 3) | 289.89 |
| Hampshire | 54 (down 10) | 48.62 |
| Middlesex East | 123 (down 38) | 110.73 |
| Middlesex North | 100 (down 21) | 90.03 |
| Middlesex South | 797 (down 35) | 717.54 |
| Middlesex West | 98 (up 7) | 88.23 |
| Norfolk | 778 (down 25) | 700.43 |
| Norfolk South | 154 (up 8) | 138.64 |
| Plymouth | 132 (down 6) | 118.84 |
| Suffolk | 607 (up 29) | 546.48 |
| Worcester | 314 (down 20) | 282.69 |
| Worcester North | 87 (down 1) | 78.32 |
| Totals | 4443 (down 120) | $4,000.00 |

ELIOT HUBBARD, JR., M.D., *Treasurer*

### SPECIAL AUTOMOBILE EMBLEM

As previously announced a special emblem has been designed for members of the Massachusetts Medical Society to fill the space on the front of the physician's automobile, formerly occupied by the front license plate. Each plate will bear an identifying number, which will be kept on record at the headquarters of the Society.

This special plate may be purchased by fellows of the Society at a cost of $2.50 without frame, or $5 with frame, on direct application to the Wildon Products Company, 20 Vernon Street, Somerville 43, Massachusetts.

ROBERT W. BUCK, *Secretary* pro tempore

### DEATH

AHERN — John F. Ahern, Sr., M.D., of Dorchester, died on March 12. He was in his sixty-fifth year.

Dr. Ahern received his degree from College of Physicians and Surgeons, Boston, in 1913. He was formerly consultant to the legal department of the city of Boston.

He is survived by his widow, a daughter and six sons.

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## BOSTON MEDICAL LIBRARY

### DEMONSTRATION OF MEDICINE IN BOSTON (1643–1896)

The practice of medicine in colonial times had more breadth than depth, for in the seventeenth century the clergy and government officials had to care for their constituents, both in body and in soul. In 1643 a physician, Ed. Stafford, of London, prepared for Governor John Winthrop a medical manual, consisting of various recipes. Ending with a code of ethics it contains a fantastic cure for the king's evil, consisting of such savory items as boiled toads. In 1862 this manual was reprinted by the

Massachusetts Historical Society with voluminous notes by Dr. Oliver Wendell Holmes. The original manuscript is shown in a current exhibition at the Boston Medical Library, with the Holmes pamphlet.

Smallpox was the great scourge of early times and inoculation of the live virus was frequently practiced. In 1721 Dr. Zabdiel Boylston, of Brookline, Massachusetts, aided and abetted by Cotton Mather, inoculated his own family. The second edition (Boston, 1730) of Boylston's pamphlet, *An historical account of the small-pox inoculation in New England*, and the tract of Cotton Mather, published anonymously in London in 1732, *An account of the method and success of inoculating the small-pox in New-England* are included in the exhibition.

Edward Jenner published his epoch-making book on vaccination in 1798 and soon after, in 1800, Benjamin Waterhouse, of Cambridge, began vaccination in Greater Boston. The Library has good collections of the works of both physicians, but currently exhibits only the important first publication of the study by Waterhouse, *A prospect of exterminating the small pox*. . .(Parts one and two, Boston, 1800 and 1802.) There was considerable doubt about the value of vaccination, and in 1809 the town of Milton conducted its famous experiment in which 13 children, all volunteers, were inoculated with smallpox and then vaccinated. None of the children, who were segregated in one house and under constant medical supervision, contracted smallpox. This was followed by a general voluntary vaccination of the townspeople and led directly to the petition of Milton to the General Court and the enactment of the Small Pox Act in 1810.

In 1843 Dr. Oliver Wendell Holmes presented his theory of the contagiousness of puerperal fever. The article was published in the *New England Quarterly Journal of Medicine and Surgery* and reprinted in the same year. He was immediately and violently opposed by Philadelphia obstetricians. This led to his second publication (Boston, 1855), "*Puerperal fever, a private pestilence*," in which he reprinted the original paper and, in twenty-four additional pages, refuted the arguments of his opponents.

In October, 1846, Dr. W. T. G. Morton publicly demonstrated the use of ether as an anesthetic at the Massachusetts General Hospital. Dr. Henry J. Bigelow wrote a description of the demonstration, entitled "Insensibility during surgical operations produced by inhalation," which was published in the *Boston Medical and Surgical Journal* for November 18, 1846. Dr. Morton refused to divulge the nature of the preparation he used, calling it Letheon, and patented it under that name. Shown in the demonstration are the *Circular. Morton's Letheon* (Boston, 1846), the first printed publication, his pamphlet *Remarks on the proper mode of administering sulphuric ether by inhalation* (Boston, 1847) and the first edition of Edward Warren's *Some account of the letheon and who was the discoverer?* (Boston, 1847).

Other items of the current exhibition include the report, published in 1850, of the Sanitary Commission of Massachusetts, headed by Lemuel Shattuck, a bookseller, recognized as a landmark in the development of public health; Francis J. Williams' work, the first comprehensive treatise of its kind in English, *The Roentgen rays in medicine and surgery* (New York, 1901), and the *Notes on X-light* (Boston, 1904), of William Rollins, a physicist, who stated in his preface that he conducted his experiments for the purpose of designing and constructing apparatus for his friend, Dr. Williams; and finally, a reprint of the epoch-making article, which won for its authors the Nobel Prize in 1934, entitled "Treatment of Pernicious Anemia by a Special Diet," by George R. Minot and William P. Murphy, which appeared in the *Journal of the American Medical Association* in 1926.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### RHEUMATIC-FEVER FELLOWSHIP

For the past four years the United States Children's Bureau has made available through the Massachusetts Department of Public Health and Harvard Medical School one fellowship in Rheumatic Fever at the House of the Good Samaritan of the Children's Medical Center. It seems likely that a fellowship will be granted for the year beginning July 1, 1953.

Trainees should be interested in working eventually in the field of rheumatic fever in public health or in teaching, rather than in private practice. Work under this fellowship will probably be acceptable for credit by the American Board of Internal Medicine or the American Board of Pediatrics.

Application should be made to Dr. Benedict F. Massell at the House of the Good Samaritan, 25 Binney Street, Boston 15, or by telephone (BEacon 2-3002).

## CORRESPONDENCE

### HOSPITALIZATION OF THE ALCOHOLIC PATIENT

*To the Editor:* I shall appreciate publication of the following letter, which I wrote to the Executive Secretary of the State Commission on Alcoholism on March 13, 1953:

> Our attention has been called to the following law:
>
> The Commonwealth shall have the care, control and treatment of all insane, feeble-minded and epileptic persons and of persons addicted to the intemperate use of narcotics or stimulants, the care of whom is vested in it by law, of each person who shall hereafter be received into any State hospital. No county, city or town shall establish or maintain any institution for the care, control and treatment of insane, feeble-minded or epileptic per-

sons or of persons addicted to the intemperate use of narcotics or stimulants, *or be liable for the board, care, treatment or act of any inmate thereof.*

Therefore, the Department of Public Welfare considers itself prohibited henceforth from assuming financial responsibility for the medically indigent in this Hospital. Inasmuch as the State hospitals refuse admission of alcoholics, except in a state of acute psychosis, this law leaves the indigent alcoholic without any provision for hospitalization.

Would the State Commission be interested in sponsoring a bill permitting the municipal departments of Public Health to contract and pay for the hospitalization of indigent addicts to alcohol and drugs?

JOSEPH THEMANN, M.D.
*Medical Director*

Washingtonian Hospital
Boston

## NOTICES

### MEMORIAL TO ANTONIO CARDARELLI

The twenty-fifth anniversary of the death of Antonio Cardarelli will be marked by the erection of monuments in the Cardarelli Hospital, Naples, and the Medical Clinic, University of Naples, by the establishment of two scholarships for young doctors in the same institutions and by the publication of books concerning his scientific works. Offerings for these memorial volumes should be addressed to Marchese Annibale Pisani Massamormile, Tesoriere delle Onoranze ad Antonio Cardarelli, Ospedale Cardarelli, Napoli, Italia.

### ACQUI RHEUMATOLOGY PRIZE

Acqui's Health Resort office announces an international competition for an original and unpublished medical article dealing with the physiopathology, clinical history and therapy of rheumatic and arthritic diseases. The competition is open to all Italian and foreign doctors. The prize of Italian Lires 1,000,000 will be awarded by the international judging commission to the best article, or may be divided between two articles. Articles may be written in Italian, French, English, Spanish and German languages.

The competition will be closed on January 31, 1954. Detailed information and the rules of the competition may be obtained from the Azienda Autonoma di Cura — Acqui, Piemonte, Italy.

### EXAMINATION FOR POSITION IN CITY OF NEW YORK

Applications for the position of chief medical director of the Board of Education, City of New York (part-time duties at an annual salary of $9050) are now being considered. Male and female graduates of approved medical schools, not over fifty years of age, licensed and registered to practice medicine in the state of New York and certified as diplomates of the American Board of Internal Medicine are qualified for examination for this position. In addition a candidate should have ten years' experience in the practice of medicine (nine months of which have been served in an internship in a hospital approved by the American Medical Association); and this experience must include or be supplemented by satisfactory administration and supervisory experience of two years (in lieu of these requirements, five years' experience as school medical inspector — personnel — in the public schools of New York City under regular license and appointment may be offered).

After examination by the Board of Examiners of the Board of Education of the City of New York, the candidate will by required to obtain a license (a fee of $10 is required on scheduling of the tests).

Further particulars may be obtained from Mr. Arthur Klein, examiner-in-charge, Board of Examiners, 110 Livingston Street, Brooklyn 1, New York.

### AWARD FOR CASE STUDIES IN RHEUMATISM

To further knowledge about patients afflicted with arthritis or rheumatism, the New England Rheumatism Society, in joint sponsorship with the Arthritis and Rheumatism Foundation, offers 10 cash prizes of $50 each for 10 case studies on rheumatic patients. Reports may be submitted by third-year and fourth-year students currently enrolled at a medical school in New England.

Reports should contain the following information: date of admission and record number of patient; pertinent clinical facts, obtained as much as possible by the author; brief consideration of the medical problem; comprehensive discussion of care, as indicated and as feasible, in the social and economic circumstances of the patient; progress notes and concluding evaluation of therapeutic program; and name, permanent address and class of author.

Reports should be typewritten and should be submitted before October 15, 1953, to Dr. Heinrich Brugsch, secretary, New England Rheumatism Society, 25 Bennet Street, Boston 11, Massachusetts. Awards will be made by a committee of the New England Rheumatism Society for studies deserving of recognition, and will be announced on December 1, 1953.

### EDWARD K. DUNHAM LECTURES

Alberto Hurtado, M.D., professor of pathological physiology, Faculty of Medicine, and research director, Institute of Andean Biology, Lima, Peru, will deliver three lectures in the amphitheater of Building D, Harvard Medical School, at 5 p.m., on the general subject "Natural Acclimatization to High Altitudes: Studies on the native resident of Morococha, Peru, at an altitude of 4,540 meters (14,900 feet)." The dates and subjects of the lectures are as follows:

Tuesday, April 21. Man at Rest.
Thursday, April 23. Man During Physical Activity.
Tuesday, April 28. General Physiological and Clinical Considerations.

### CUTTER LECTURE ON PREVENTIVE MEDICINE

The Harvard School of Public Health announces that on May 6 at 5 p.m., Sir Gordon Covell, director, Malaria Laboratory, Horton Hospital, Epsom, England, adviser on malaria to the Ministry of Health and former director of the Malaria Institute of India, will deliver the Cutter Lecture on Preventive Medicine in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston. His subject will be "Current Research toward a Global Control of Malaria." The medical profession, medical and public-health students and others interested are cordially invited to attend.

### HAMPDEN DISTRICT MEDICAL SOCIETY

The annual meeting of the Hampden District Medical Society will be held at Rovelli's, Springfield, on Tuesday, April 28, at 6:30 p.m. Speaker "You will be surprised."

### MASSACHUSETTS SCHOOL PHYSICIANS' ASSOCIATION

The annual meeting of the Massachusetts School Physicians' Association will be held at the Hotel Statler, Boston, on Wednesday, May 20. After a business meeting at 1 p.m., the following clinical program will be presented:

2:30 p.m. Common Ligament Injuries Sustained in Competitive Athletics (Blackboard presentation and Lantern Slides). Dr. Augustus Thorndike.
3:15 p.m. School Psychiatry. Dr. Richmond Holder.

Dr. J. Roswell Gallagher, Director, Adolescent Clinic, Children's Medical Center, will lead the discussion. Dr. Francis F. Cary, president of the Association, will introduce the speakers.

### NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held in the auditorium of the New England Medical Center, 171 Harrison Avenue, Boston, on Wednesday, April 15, at 8 p.m. Dr. Arthur A. Thibodeau, M.D., chief of orthopedic surgery, New England Center Hospital and associate professor of orthopedic surgery, Tufts College Medical School, will speak on the subject "The Evaluation and Treatment of a Patient with Low-Back Pain."

A general discussion will follow. (An important meeting of the Council will be held at 7:30 p.m.)

Physicians, rehabilitation personnel and students are cordially invited to attend.

## NEW ENGLAND SOCIETY OF PSYCHIATRY

The annual meeting of the New England Society of Psychiatry will be held at New Hampshire State Hospital, Concord, New Hampshire, on Wednesday, April 22.

PROGRAM

11:30 a.m.–12:30 p.m. Tour of the hospital with host to Society, Dr. John L. Smalldon.

11:30 a.m.–12:30 p.m. Executive-committee meeting.

12:30–1:00 p.m. Business meeting.

1:00 p.m. Luncheon. (A nominal charge of $1 will be made for the luncheon.)

2:00 p.m. Pseudoneurotic Schizophrenia. Dr. Paul H. Hoch, principal research psychiatrist, New York State Psychiatric Institute.

## NATIONAL TUBERCULOSIS ASSOCIATION

The annual meeting of the National Tuberculosis Association will be held in the Statler and Biltmore hotels, Los Angeles, May 18–22. This will be a joint session of the Association with the American Trudeau Society and the National Conference of Tuberculosis Workers. The program will include medical sessions, luncheon meetings, panels and seminars.

## AMERICAN ACADEMY OF PEDIATRICS

The 1953 areal meeting of the American Academy of Pediatrics will be held at the Hotel Statler, Boston, April 20, 21 and 22. General scientific sessions will be held daily in the Grand Ballroom on April 20 and 21 and on the morning of April 22. Subjects to be discussed are as follows:

Monday, April 20. Antibiotics and Chemotherapy in Pediatric Practice. ACTH and Cortisone, Their Effects and Clinical Uses.

Tuesday, April 21. Orthopedics and the Pediatrician. Parenteral Fluid Therapy.

Wednesday, April 22. Recent Knowledge on Poliomyelitis.

Practitioners wishing to attend should communicate with the Executive Secretary, Dr. E. H. Christopherson, 610 Church St., Evanston, Illinois. Residents, interns and medical students are welcome as guests, and should present identifying credentials at the registration desk on the mezzanine.

## AMERICAN ACADEMY OF DENTAL MEDICINE

The seventh annual meeting of the American Academy of Dental Medicine will be held at the Shoreham Hotel, Washington, D. C., June 26–28, 1953. Nutrition will be the theme of the meeting.

A program of sightseeing and entertainment is also being arranged. All members and interested dentists and physicians are cordially invited to attend. Full details as well as reservations are available through the National Secretary, Dr. William M. Greenhut, 124 East 84th Street, New York 28, New York.

## SEVENTH ANNUAL ROCKY MOUNTAIN CANCER CONFERENCE

The seventh annual Rocky Mountain Cancer Conference will be held in Denver on July 8 and 9. As in previous years there will be eight outstanding guest speakers, and on the first evening a banquet and entertainment for both the doctors and their wives. There is no registration fee for this conference.

## SOCIETY MEETINGS AND CONFERENCES

APRIL 9–27. Consultation Clinics for Crippled Children in Massachusetts. Page 523, issue of March 19.

APRIL 14. Harvard Medical Society. Page 619, issue of April 2.

APRIL 14. New York Society for Circulatory Diseases and New York Cardiological Society. Page 528, issue of March 19.

APRIL 15. New England Society of Physical Medicine. Page 663.

APRIL 15. Massachusetts Academy of General Practice. Page 480, issue of March 12.

APRIL 16–18. Postgraduate Course in Obstetrics and Pediatrics. Page 525, issue of March 19.

APRIL 17. Phi Delta Epsilon Lecture. Page 620, issue of April 2.

APRIL 19–24. National Industrial Health Conference. Page 308, issue of February 12.

APRIL 20. Hartford Medical Society. Page 42, issue of January 1.

APRIL 20–22. American Academy of Pediatrics. Notice above.

APRIL 20–MAY 6. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

APRIL 21. South End Medical Club. Page 570, issue of March 26.

APRIL 21, 23 AND 28. Edward K. Dunham Lectures. Page 663.

APRIL 22. New England Society of Psychiatry. Notice above.

APRIL 22. Middlesex South District Medical Society. Page 620, issue of April 2.

APRIL 24–29. American College of Allergists. Page 570, issue of March 26.

APRIL 25. Boston City Hospital Alumni Association. Page 570, issue of March 26.

APRIL 25. Alumni Association of the State University College of Medicine at New York City. Page 396, issue of February 26.

APRIL 25. Graduate Club of Boston. Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

APRIL 28. Hampden District Medical Society. Page 663.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

MAY 2. When Is the Treatment of Mitral Stenosis Surgical? Drs. Laurence B. Ellis and Dwight E. Harken. Mount Auburn Hospital, Cambridge. 10:05 a.m.

MAY 6. Cutter Lecture on Preventive Medicine. Page 663.

MAY 7–9. American Goiter Association. Page 480, issue of March 12.

MAY 11–13. Aero Medical Association. Page 526, issue of March 19.

MAY 18–22. National Tuberculosis Association. Notice above.

MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 20. Massachusetts School Physicians' Association. Page 663.

MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

MAY 30 AND 31. Society for Investigative Dermatology, Inc. Page 570, issue of March 26.

JUNE 7–9. American College of Cardiology. Page 395, issue of February 26.

JUNE 26–28. American Academy of Dental Medicine. Notice above.

JUNE 28–JULY 2. American Society of X-Ray Technicians. Page 480, issue of March 12.

JULY 8 AND 9. Seventh Annual Rocky Mountain Cancer Conference. Notice above.

### DISTRICT MEDICAL SOCIETIES

**ESSEX NORTH**

MAY 13. Andover Country Club, Shawsheen.

**HAMPDEN**

APRIL 28. Rovelli's, Springfield, 6:30 p.m.

**MIDDLESEX SOUTH**

APRIL 22.

**WORCESTER**

MAY 6. Annual Meeting. Sheraton Hotel. Dr. Louis H. Bauer, President, American Medical Association.

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 16

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*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, APRIL 17

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

*(Notices concluded on page xv)*